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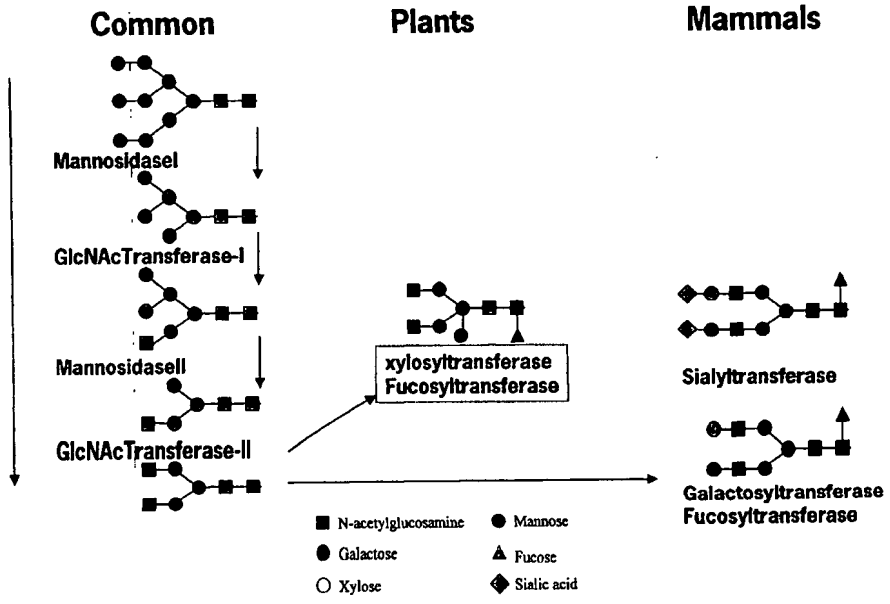

(57) Abstract: The invention is directed to methods for optimizing glycan processing in organisms (and in particular, plants) so that a glycoprotein having complex type bi-antennary glycans and thus 5 containing galactose residues on both arms and which are devoid of (or reduce in) xylose and fucose can be obtained. The invention is further directed to said glycoprotein obtained and host system comprising said protein.

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OPTIMIZING GLYCAN PROCESSING IN PLANTS

FIELD OF THE INVENTION

The invention is directed to methods for optimizing glycan processing of cell or an organism containing glycoproteins with N-glycans, in particular plants so that a glycoprotein having an N-glycan, high mannose type, hybrid or preferably complex type N-glycans, including but not limited to bi-antennary N-glycans, and containing a galactose residue on at least one arm of the N-glycan and which are devoid of (or reduced in) xylose and fucose residues can be obtained. The invention is further directed to said glycoprotein obtained and in particular a plant host system comprising said protein.

BACKGROUND OF THE INVENTION

N-linked glycans, specific oligosaccharide structures attached to asparagine residues of glycoproteins, can contribute significantly to the properties of the protein and, in turn, to the properties of the organism. Plant proteins can carry N-linked glycans but in marked contrast to mammals only few biological processes are known to which they contribute.

Biogenesis of N-linked glycans begins with the synthesis of a lipid linked oligosaccharide moiety (Glc3Man9GlcNAc2-) which is transferred en bloc to the nascent polypeptide chain in the endoplasmic reticulum (ER). Through a series of trimming reactions by exoglycosidases in the ER and cis-Golgi compartments, the so-called "high mannose" (Man9GlcNAc2 to Man5GlcNAc2) glycans are formed. Subsequently, the formation of complex type glycans starts with the transfer of the first GlcNAc onto Man5GlcNAc2 by GnTI and further trimming by mannosidase II (ManII) to form GlcNAcMan3GlcNAc2. Complex glycan biosynthesis continues while the glycoprotein is progressing through the secretory pathway with the transfer in the Golgi apparatus of the second GlcNAc residue by GnTII as well as other monosaccharide residues onto the GlcNAcMan3GlcNAc2 under the action of several other glycosyl transferases.

Plants and mammals differ with respect to the formation of complex glycans (see Figure 1, which compares the glycosylation pathway of glycoproteins in plants and mammals). In plants, complex glycans are characterized by the presence of β(1,2)-xylose residues linked to the Man-3 and/or an α(1,3)-fucose residue linked to GlcNAc-1, instead of an α(1,6)-fucose residue linked to the GlcNAc-1. Genes encoding the corresponding xylosyl (XylT) and fucosyl (FucT) transferases have been isolated [Strasser *et al.*, "Molecular cloning and functional expression of beta1,2-xylosyltransferase cDNA from Arabidopsis thaliana," *FEBS Lett.* 472:105 (2000); Leiter *et al.*, "Purification, cDNA cloning, and expression of GDP-L-Fuc:Asn-linked GlcNAc alpha 1,3-fucosyltransferase from mung beans," *J. Biol. Chem.* 274:21830 (1999)]. Plants do not possess β(1,4)-galactosyltransferases nor α(2,6)sialyltransferases and consequently plant glycans lack the β(1,4)-galactose and terminal α(2,6)NeuAc residues often found on mammalian glycans.

The final glycan structures are not only determined by the mere presence of enzymes involved in their biosynthesis and transport but to a large extent by the specific sequence of the various enzymatic reactions. The latter is controlled by discrete sequestering and relative position of these enzymes throughout the ER and Golgi, which is mediated by the interaction of determinants of the transferase and specific characteristics of the sub-Golgi compartment for which the transferase is destined. A number of studies using hybrid molecules have identified that the transmembrane domains of several glycosyltransferases, including that of β(1,4)-galactosyltransferases, play a central role in their sub-Golgi sorting [Grabenhorst *et al.*, *J. Biol. Chem* 274:36107 (1999); Colley, K., *Glycobiology* 7:1 (1997); Munro, S., *Trends Cell Biol.* 8:11 (1998); Gleeson, P.A., *Histochem. Cell Biol.* 109:517 (1998)].

Although plants and mammals have diverged a relatively long time ago, N-linked glycosylation seems at least partly conserved. This is evidenced by the similar though not identical glycan structures and by the observation that a mammalian GlcNAcTI gene complements a Arabidopsis mutant that is deficient in GlcNAcTI activity, and vice versa. The differences in glycan structures can have important consequences. For example, xylose and α(1,3)-fucose epitopes are known to be highly immunogenic and possibly allergenic in some circumstances, which may pose a problem when plants are used for the production of therapeutic glycoproteins. Moreover, blood serum of many allergy patients contains IgE directed against these epitopes but also 50% of non-allergic blood donors contains in their sera antibodies specific for core-xylose whereas 25% have antibodies for core-alpha 1,3-fucose (Bardor *et al.*, 2002, in press, *Glycobiology*) (Advance Access published December 17, 2002) which make these individuals at risk to treatments with recombinant proteins produced in plants containing fucose and/or xylose. In addition, this carbohydrate directed IgE in sera might cause false positive reaction in *in vitro* tests using plant extracts since there is evidence that these carbohydrate specific IgE's are not relevant for the allergenic reaction. In sum, a therapeutic failure with a glycoprotein produced in plants might be the result of accelerated clearance of the recombinant glycoprotein having xylose and/or fucose.

Accordingly, there is a need to better control glycosylation in plants, and particularly, glycosylation of glycoproteins intended for therapeutic use.

DEFINITIONS

To facilitate understanding of the invention, a number of terms as used in this specification are defined below.

The term "vector" refers to any genetic element, such as a plasmid, phage, transposon, cosmid, chromosome, retrovirus, virion, or similar genetic element, which is capable of replication when associated with the proper control elements and which can transfer gene sequences into cells and/or between cells. Thus, this term includes cloning and expression vehicles, as well as viral vectors.

The term "expression vector" as used herein refers to a recombinant DNA molecule containing a desired coding sequence (or coding sequences) – such as the coding sequence(s) for the hybrid enzyme(s) described in more detail below - and appropriate nucleic acid sequences necessary for the expression of the operably linked coding sequence in a particular host cell or organism. Nucleic acid sequences necessary for expression in prokaryotes usually include a promoter, an operator (optional), and a ribosome binding site, often along with other sequences. Eukaryotic cells are known to utilize promoters, enhancers, and termination and polyadenylation signals. It is not intended that the present invention be limited to particular expression vectors or expression vectors with particular elements.

The term "transgenic" when used in reference to a cell refers to a cell which contains a transgene, or whose genome has been altered by the introduction of a transgene. The term "transgenic" when used in reference to a cell, tissue or to a plant refers to a cell, tissue or plant, respectively, which comprises a transgene, where one or more cells of the tissue contain a transgene (such as a gene encoding the hybrid enzyme(s) of the present invention), or a plant whose genome has been altered by the introduction of a transgene. Transgenic cells, tissues and plants may be produced by several methods including the introduction of a "transgene" comprising nucleic acid (usually DNA) into a target cell or integration of the transgene into a chromosome of a target cell by way of human intervention, such as by the methods described herein.

The term "transgene" as used herein refers to any nucleic acid sequence which is introduced into the genome of a cell by experimental manipulations. A transgene may be an "endogenous DNA sequence," or a "heterologous DNA sequence" (*i.e.*, "foreign DNA"). The term "endogenous DNA sequence" refers to a nucleotide sequence which is naturally found in the cell into which it is introduced so long as it does not contain some modification (*e.g.*, a point mutation, the presence of a selectable marker gene, or other like modifications) relative to the naturally-occurring sequence. The term "heterologous DNA sequence" refers to a nucleotide sequence which is ligated to, or is manipulated to become ligated to, a nucleic acid sequence to which it is not ligated in nature, or to which it is ligated at a different location in nature. Heterologous DNA is not endogenous to the cell into which it is introduced, but has been obtained from another cell. Heterologous DNA also includes an endogenous DNA sequence which contains some modification. Generally, although not necessarily, heterologous DNA encodes RNA and proteins that are not normally produced by the cell into which it is expressed. Examples of heterologous DNA include reporter genes, transcriptional and translational regulatory sequences, selectable marker proteins (*e.g.*, proteins which confer drug resistance), or other similar elements.

The term "foreign gene" refers to any nucleic acid (*e.g.*, gene sequence) which is introduced into the genome of a cell by experimental manipulations and may include gene sequences found in that cell so long as the introduced gene contains some modification (*e.g.*, a point mutation, the presence of a selectable marker gene, or other like modifications) relative to the naturally-occurring gene.

The term "fusion protein" refers to a protein wherein at least one part or portion is from a first protein and another part or portion is from a second protein. The term "hybrid enzyme" refers to a fusion protein which is a functional enzyme, wherein at least one part or portion is from a first species and another part or portion is from a second species. Preferred hybrid enzymes of the present invention are functional glycosyltransferases (or portions thereof) wherein at least one part or portion is from a plant and another part or portion is from a mammal (such as human).

The term "introduction into a cell" or "introduction into a host cell" in the context of nucleic acid (*e.g.*, vectors) is intended to include what the art calls "transformation" or "transfection" or "transduction." Transformation of a cell may be stable or transient – and the present invention contemplates introduction of vectors under conditions where, on the one hand, there is stable expression, and on the other hand, where there is only transient expression. The term "transient transformation" or "transiently transformed" refers to the introduction of one or more transgenes into a cell in the absence of integration of the transgene into the host cell's genome. Transient transformation may be detected by, for example, enzyme-linked immunosorbent assay (ELISA) which detects the presence of a polypeptide encoded by one or more of the transgenes. Alternatively, transient transformation may be detected by detecting the activity of the protein (*e.g.*, antigen binding of an antibody) encoded by the transgene (*e.g.*, the antibody gene). The term "transient transformant" refers to a cell which has transiently incorporated one or more transgenes. In contrast, the term "stable transformation" or "stably transformed" refers to the introduction and integration of one or more transgenes into the genome of a cell. Stable transformation of a cell may be detected by Southern blot hybridization of genomic DNA of the cell with nucleic acid sequences which are capable of binding to one or more of the transgenes. Alternatively, stable transformation of a cell may also be detected by the polymerase chain reaction (PCR) of genomic DNA of the cell to amplify transgene sequences. The term "stable transformant" refers to a cell which has stably integrated one or more transgenes into the genomic DNA. Thus, a stable transformant is distinguished from a transient transformant in that, whereas genomic DNA from the stable transformant contains one or more transgenes, genomic DNA from the transient transformant does not contain a transgene.

The term "host cell" includes both mammalian (e.g. human B cell clones, Chinese hamster ovary cells, hepatocytes) and non-mammalian cells (*e.g.* insect cells, bacterial cells, plant cells). In one embodiment, the host cells are mammalian cells and the introduction of a vector expressing a hybrid protein of the present invention (e.g TmGnTII-GalT) inhibits (or at least reduces) fucosylation in said mammalian cells.

The term "nucleotide sequence of interest" refers to any nucleotide sequence, the manipulation of which may be deemed desirable for any reason (*e.g.*, confer improved qualities, use for production of therapeutic proteins), by one of ordinary skill in the art. Such nucleotide sequences include, but are not limited to, coding sequences of structural genes (*e.g.*, reporter genes, selection marker genes, oncogenes, antibody genes, drug resistance genes, growth factors, and other like genes), and non-coding regulatory sequences which do not encode an mRNA or protein product,

(*e.g.*, promoter sequence, polyadenylation sequence, termination sequence, enhancer sequence, and other like sequences). The present invention contemplates host cells expressing a heterologous protein encoded by a nucleotide sequence of interest along with one or more hybrid enzymes.

The term "isolated" when used in relation to a nucleic acid, as in "an isolated nucleic acid sequence" refers to a nucleic acid sequence that is identified and separated from one or more other components (*e.g.*, separated from a cell containing the nucleic acid, or separated from at least one contaminant nucleic acid, or separated from one or more proteins, one or more lipids) with which it is ordinarily associated in its natural source. Isolated nucleic acid is nucleic acid present in a form or setting that is different from that in which it is found in nature. In contrast, non-isolated nucleic acids are nucleic acids such as DNA and RNA which are found in the state they exist in nature. For example, a given DNA sequence (*e.g.*, a gene) is found on the host cell chromosome in proximity to neighboring genes; RNA sequences, such as a specific mRNA sequence encoding a specific protein, are found in the cell as a mixture with numerous other mRNAs which encode a multitude of proteins. However, an isolated nucleic acid sequence comprising SEQ ID NO:1 includes, by way of example, such nucleic acid sequences in cells which ordinarily contain SEQ ID NO:1 where the nucleic acid sequence is in a chromosomal or extrachromosomal location different from that of natural cells, or is otherwise flanked by a different nucleic acid sequence than that found in nature. The isolated nucleic acid sequence may be present in single-stranded or double-stranded form. When an isolated nucleic acid sequence is to be utilized to express a protein, the nucleic acid sequence will contain at a minimum at least a portion of the sense or coding strand (*i.e.*, the nucleic acid sequence may be single-stranded). Alternatively, it may contain both the sense and anti-sense strands (*i.e.*, the nucleic acid sequence may be double-stranded).

As used herein, the term "purified" refers to molecules, either nucleic or amino acid sequences, that are removed from their natural environment, isolated or separated. An "isolated nucleic acid sequence" is therefore a purified nucleic acid sequence. "Substantially purified" molecules are at least 60% free, preferably at least 75% free, and more preferably at least 90% free, from other components with which they are naturally associated. The present invention contemplates both purified (including substantially purified) and unpurified hybrid enzyme(s) (which are described in more detail below).

As used herein, the terms "complementary" or "complementarity" are used in reference to nucleotide sequences related by the base-pairing rules. For example, the sequence 5'-AGT-3' is complementary to the sequence 5'-ACT-3'. Complementarity can be "partial" or "total." "Partial" complementarity is where one or more nucleic acid bases is not matched according to the base pairing rules. "Total" or "complete" complementarity between nucleic acids is where each and every nucleic acid base is matched with another base under the base pairing rules. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of hybridization between nucleic acid strands.

A "complement" of a nucleic acid sequence as used herein refers to a nucleotide sequence whose nucleic acids show total complementarity to the nucleic acids of the nucleic acid sequence. For example, the present invention contemplates the complements of SEQ ID NOS: 1, 3, 5, 9, 27, 28, 29, 30, 31, 32, 33, 34, 35, 37, 38, 40, 41 and 43.

The term "homology" when used in relation to nucleic acids refers to a degree of complementarity. There may be partial homology (*i.e.*, partial identity) or complete homology (*i.e.*, complete identity). A partially complementary sequence is one that at least partially inhibits a completely complementary sequence from hybridizing to a target nucleic acid and is referred to using the functional term "substantially homologous." The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or Northern blot, solution hybridization and the like) under conditions of low stringency. A substantially homologous sequence or probe (*i.e.*, an oligonucleotide which is capable of hybridizing to another oligonucleotide of interest) will compete for and inhibit the binding (*i.e.*, the hybridization) of a completely homologous sequence to a target under conditions of low stringency. This is not to say that conditions of low stringency are such that non-specific binding is permitted; low stringency conditions require that the binding of two sequences to one another be a specific (*i.e.*, selective) interaction. The absence of non-specific binding may be tested by the use of a second target which lacks even a partial degree of complementarity (*e.g.*, less than about 30% identity); in the absence of non-specific binding the probe will not hybridize to the second non-complementary target.

When used in reference to a double-stranded nucleic acid sequence such as a cDNA or genomic clone, the term "substantially homologous" refers to any probe which can hybridize to either or both strands of the double-stranded nucleic acid sequence under conditions of low stringency as described *infra*.

When used in reference to a single-stranded nucleic acid sequence, the term "substantially homologous" refers to any probe which can hybridize to the single-stranded nucleic acid sequence under conditions of low stringency as described *infra*.

The term "hybridization" as used herein includes "any process by which a strand of nucleic acid joins with a complementary strand through base pairing." [Coombs J (1994) *Dictionary of Biotechnology*, Stockton Press, New York NY]. Hybridization and the strength of hybridization (*i.e.*, the strength of the association between the nucleic acids) is impacted by such factors as the degree of complementarity between the nucleic acids, stringency of the conditions involved, the T_m of the formed hybrid, and the G:C ratio within the nucleic acids.

As used herein, the term "T_m" is used in reference to the "melting temperature." The melting temperature is the temperature at which a population of double-stranded nucleic acid molecules becomes half dissociated into single strands. The equation for calculating the T_m of nucleic acids is well known in the art. As indicated by standard references, a simple estimate of the T_m value may be calculated by the equation: $T_m = 81.5 + 0.41(\% G + C)$, when a nucleic acid is in aqueous solution

at 1 M NaCl [*see e.g.*, Anderson and Young, Quantitative Filter Hybridization, in: *Nucleic Acid Hybridization* (1985)]. Other references include more sophisticated computations which take structural as well as sequence characteristics into account for the calculation of T_m.

Low stringency conditions when used in reference to nucleic acid hybridization comprise conditions equivalent to binding or hybridization at 68°C in a solution consisting of 5X SSPE (Saline, Sodium Phosphate, EDTA) (43.8 g/l NaCl, 6.9 g/l $NaH_2PO_4 \cdot H_2O$ and 1.85 g/l EDTA (Ethylenediaminetetracetic Acid), pH adjusted to 7.4 with NaOH), 0.1% SDS (Sodium dodecyl sulfate), 5X Denhardt's reagent [50X Denhardt's contains the following per 500 ml: 5 g Ficoll (Type 400, Pharmacia), 5 g BSA (Bovine Serum Albumin) (Fraction V; Sigma)] and 100 µg/ml denatured salmon sperm DNA followed by washing in a solution comprising between 0.2X and 2.0X SSPE, and 0.1% SDS at room temperature when a DNA probe of about 100 to about 1000 nucleotides in length is employed.

High stringency conditions when used in reference to nucleic acid hybridization comprise conditions equivalent to binding or hybridization at 68°C in a solution consisting of 5X SSPE, 1% SDS, 5X Denhardt's reagent and 100 µg/ml denatured salmon sperm DNA followed by washing in a solution comprising 0.1X SSPE, and 0.1% SDS at 68°C when a probe of about 100 to about 1000 nucleotides in length is employed.

The term "equivalent" when made in reference to a hybridization condition as it relates to a hybridization condition of interest means that the hybridization condition and the hybridization condition of interest result in hybridization of nucleic acid sequences which have the same range of percent (%) homology. For example, if a hybridization condition of interest results in hybridization of a first nucleic acid sequence with other nucleic acid sequences that have from 50% to 70% homology to the first nucleic acid sequence, then another hybridization condition is said to be equivalent to the hybridization condition of interest if this other hybridization condition also results in hybridization of the first nucleic acid sequence with the other nucleic acid sequences that have from 50% to 70% homology to the first nucleic acid sequence.

When used in reference to nucleic acid hybridization the art knows well that numerous equivalent conditions may be employed to comprise either low or high stringency conditions; factors such as the length and nature (DNA, RNA, base composition) of the probe and nature of the target (DNA, RNA, base composition, present in solution or immobilized) and the concentration of the salts and other components (*e.g.*, the presence or absence of formamide, dextran sulfate, polyethylene glycol) are considered and the hybridization solution may be varied to generate conditions of either low or high stringency hybridization different from, but equivalent to, the above-listed conditions.

The term "promoter," "promoter element," or "promoter sequence" as used herein, refers to a DNA sequence which when ligated to a nucleotide sequence of interest is capable of controlling the transcription of the nucleotide sequence of interest into mRNA. A promoter is typically, though not necessarily, located 5' (*i.e.*, upstream) of a nucleotide sequence of interest whose transcription into

mRNA it controls, and provides a site for specific binding by RNA polymerase and other transcription factors for initiation of transcription.

Promoters may be tissue specific or cell specific. The term "tissue specific" as it applies to a promoter refers to a promoter that is capable of directing selective expression of a nucleotide sequence of interest to a specific type of tissue (*e.g.*, petals) in the relative absence of expression of the same nucleotide sequence of interest in a different type of tissue (*e.g.*, roots). Tissue specificity of a promoter may be evaluated by, for example, operably linking a reporter gene to the promoter sequence to generate a reporter construct, introducing the reporter construct into the genome of a plant such that the reporter construct is integrated into every tissue of the resulting transgenic plant, and detecting the expression of the reporter gene (*e.g.*, detecting mRNA, protein, or the activity of a protein encoded by the reporter gene) in different tissues of the transgenic plant. The detection of a greater level of expression of the reporter gene in one or more tissues relative to the level of expression of the reporter gene in other tissues shows that the promoter is specific for the tissues in which greater levels of expression are detected. The term "cell type specific" as applied to a promoter refers to a promoter which is capable of directing selective expression of a nucleotide sequence of interest in a specific type of cell in the relative absence of expression of the same nucleotide sequence of interest in a different type of cell within the same tissue. The term "cell type specific" when applied to a promoter also means a promoter capable of promoting selective expression of a nucleotide sequence of interest in a region within a single tissue. Cell type specificity of a promoter may be assessed using methods well known in the art, *e.g.*, immuno-histochemical staining. Briefly, tissue sections are embedded in paraffin, and paraffin sections are reacted with a primary antibody which is specific for the polypeptide product encoded by the nucleotide sequence of interest whose expression is controlled by the promoter. A labeled (*e.g.*, peroxidase conjugated) secondary antibody which is specific for the primary antibody is allowed to bind to the sectioned tissue and specific binding detected (*e.g.*, with avidin/biotin) by microscopy.

Promoters may be constitutive or regulatable. The term "constitutive" when made in reference to a promoter means that the promoter is capable of directing transcription of an operably linked nucleic acid sequence in the absence of a stimulus (*e.g.*, heat shock, chemicals, light, or similar stimuli). Typically, constitutive promoters are capable of directing expression of a transgene in substantially any cell and any tissue. In contrast, a "regulatable" promoter is one which is capable of directing a level of transcription of an operably linked nuclei acid sequence in the presence of a stimulus (*e.g.*, heat shock, chemicals, light, or similar stimuli) which is different from the level of transcription of the operably linked nucleic acid sequence in the absence of the stimulus.

The terms "infecting" and "infection" with a bacterium refer to co-incubation of a target biological sample, (*e.g.*, cell, tissue, plant part) with the bacterium under conditions such that nucleic acid sequences contained within the bacterium are introduced into one or more cells of the target biological sample.

The term "*Agrobacterium*" refers to a soil-borne, Gram-negative, rod-shaped phytopathogenic bacterium which causes crown gall. The term "*Agrobacterium*" includes, but is not limited to, the strains *Agrobacterium tumefaciens*, (which typically causes crown gall in infected plants), and *Agrobacterium rhizogens* (which causes hairy root disease in infected host plants). Infection of a plant cell with *Agrobacterium* generally results in the production of opines (*e.g.*, nopaline, agropine, octopine) by the infected cell. Thus, *Agrobacterium* strains which cause production of nopaline (*e.g.*, strain LBA4301, C58, A208) are referred to as "nopaline-type" *Agrobacteria*; *Agrobacterium* strains which cause production of octopine (*e.g.*, strain LBA4404, Ach5, B6) are referred to as "octopine-type" *Agrobacteria*; and *Agrobacterium* strains which cause production of agropine (*e.g.*, strain EHA105, EHA101, A281) are referred to as "agropine-type" *Agrobacteria*.

The terms "bombarding, "bombardment," and "biolistic bombardment" refer to the process of accelerating particles towards a target biological sample (*e.g.*, cell, tissue, plant part – such as a leaf, or intact plant) to effect wounding of the cell membrane of a cell in the target biological sample and/or entry of the particles into the target biological sample. Methods for biolistic bombardment are known in the art (*e.g.*, U.S. Patent Nos. 5,584,807 and 5,141,131, the contents of both are herein incorporated by reference), and are commercially available (*e.g.*, the helium gas-driven microprojectile accelerator (PDS-1000/He) (BioRad).

The term "microwounding" when made in reference to plant tissue refers to the introduction of microscopic wounds in that tissue. Microwounding may be achieved by, for example, particle bombardment as described herein. The present invention specifically contemplates schemes for introducing nucleic acid which employ microwounding.

The term "organism" as used herein refers to all organisms and in particular organisms containing glycoproteins with n-linked glycans.

The term "plant" as used herein refers to a plurality of plant cells which are largely differentiated into a structure that is present at any stage of a plant's development. Such structures include, but are not limited to, a fruit, shoot, stem, root, leaf, seed, flower petal, or similar structure. The term "plant tissue" includes differentiated and undifferentiated tissues of plants including, but not limited to, roots, shoots, leaves, pollen, seeds, tumor tissue and various types of cells in culture (*e.g.*, single cells, protoplasts, embryos, callus, protocorm-like bodies, and other types of cells). Plant tissue may be *in planta*, in organ culture, tissue culture, or cell culture. Similarly, "plant cells" may be cells in culture or may be part of a plant.

Glycosyltransferases are enzymes that catalyze the processing reactions that determine the structures of cellular oligosaccharides, including the oligosaccharides on glycoproteins. As used herein, "glycosyltransferase" is meant to include mannosidases, even though these enzymes trim glycans and do not "transfer" a monosaccharide. Glycosyltransferases share the feature of a type II membrane orientation. Each glycosyltransferase is comprised of an amino terminal cytoplasmic tail (shown for illustration purposes below as a made up of a string of amino acids arbitrarily labeled "X"

– without intending to suggest the actual size of the region), a signal anchor domain (shown below as made up of a string of amino acids labeled "H" for hydrophobic – without intending to suggest the actual size of the domain and without intending to suggest that the domain is only made up of hydrophobic amino acids) that spans the membrane (referred to herein as a "transmembrane domain"), followed by a luminal stem (shown below as made up of a string of amino acids arbitrarily labeled "S" – without intended to suggest the actual size of the region) or stalk region, and a carboxy-terminal catalytic domain (shown below as made up of a string of amino acids arbitrarily labeled "C" – without intending to suggest the actual size of the domain:

NH_2-XXXXXXXHHHHHHHHHSSSSSSSSCCCCCCCC

Collectively, The Cytoplasmic Tail-Transmembrane-Stem Region or "CTS" (which has been underlined in the above schematic for clarity) can be used (or portions thereof) in embodiments contemplated by the present invention wherein the catalytic domain is exchanged or "swapped" with a corresponding catalytic domain from another molecule (or portions of such regions/domains) to create a hybrid protein.

For example, in a preferred embodiment, the present invention contemplates nucleic acid encoding a hybrid enzyme (as well as vectors containing such nucleic acid, host cells containing such vectors, and the hybrid enzyme itself), said hybrid enzyme comprising at least a portion of a CTS region [*e.g.*, the cytoplasmic tail ("C"), the transmembrane domain ("T"), the cytoplasmic tail together with the transmembrane domain ("CT"), the transmembrane domain together with the stem ("TS"), or the complete CTS region] of a first glycosyltransferase (*e.g.* plant glycosyltransferase) and at least a portion of a catalytic region of a second glycosyltransferase (*e.g.* mammalian glycosyltransferase). To create such an embodiment, the coding sequence for the entire CTS region (or portion thereof) may be deleted from nucleic acid coding for the mammalian glycosyltransferase and replaced with the coding sequence for the entire CTS region (or portion thereof) of a plant glycosyltransferase. On the other hand, a different approach might be taken to create this embodiment; for example, the coding sequence for the entire catalytic domain (or portion thereof) may be deleted from the coding sequence for the plant glycosyltransferase and replaced with the coding sequence for the entire catalytic domain (or portion thereof) of the mammalian glycosyltransferase. In such a case, the resulting hybrid enzyme would have the amino-terminal cytoplasmic tail of the plant glycosyltransferase linked to the plant glycosyltransferase transmembrane domain linked to the stem region of the plant glycosyltransferase in the normal manner of the wild-type plant enzyme – but the stem region would be linked to the catalytic domain of the mammalian glycosyltransferase (or portion thereof).

It is not intended that the present invention be limited only to the two approaches outlined above. Other variations in the approach are contemplated. For example, to create nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising at least a portion of a transmembrane region of a plant glycosyltransferase and at least a portion of a catalytic region of a mammalian

glycosyltransferase, one might use less than the entire coding sequence for the CTS region (*e.g.*, only the transmembrane domain of the plant glycosytransferase, or the complete cytoplasmic tail together with all or a portion of the transmembrane domain, or the complete cytoplasmic tail together with all of the transmembrane domain together with a portion of the stem region). One might delete the mammalian coding sequence for the entire cytoplasmic tail together with the coding sequence for the transmembrane domain (or portion thereof) – followed by replacement with the corresponding coding sequence for the cytoplasmic tail and transmembrane domain (or portion thereof) of the plant glycosyltransferase. In such a case, the resulting hybrid enzyme would have the stem region of the mammalian glycosyltransferase linked to the plant glycosyltransferase transmembrane domain (or portion thereof) which in turn would be linked to the amino-terminal cytoplasmic tail of the plant glycosyltransferase, with the stem region being linked to the catalytic domain of the mammalian glycosyltransferase (i.e. two of the four regions/domains would be of plant origin and two would be of mammalian origin).

In other embodiments, the present invention contemplates nucleic acid encoding a hybrid enzyme (along with vectors, host cells containing the vectors, plants – or plant parts - containing the host cells), said hybrid enzyme comprising at least a portion of an amino-terminal cytoplasmic tail of a plant glycosyltransferase and at least a portion of a catalytic region of a mammalian glycosyltransferase. In this embodiment, the hybrid enzyme encoded by the nucleic acid might or might not contain other plant sequences (*e.g.*, the transmembrane domain or portion thereof, the stem region or portion thereof). For example, to create such an embodiment, the coding sequence for the entire cytoplasmic tail (or portion thereof) may be deleted from nucleic acid coding for the mammalian glycosyltransferase and replaced with the coding sequence for the entire cytoplasmic domain (or portion thereof) of a plant glycosyltransferase. In such a case, the resulting hybrid enzyme would have the amino-terminal cytoplasmic tail (or portion thereof) of the plant glycosyltransferase linked to the mammalian glycosyltransferase transmembrane domain, which in turn is linked to stem region of the mammalian glycosyltransferase, the stem region being linked to the catalytic domain of the mammalian glycosyltransferase. On the other hand, a different approach might be taken to create this embodiment; for example, the coding sequence for the entire catalytic domain (or portion thereof) may be deleted from the coding sequence for the plant glycosyltransferase and replaced with the coding sequence for the entire catalytic domain (or portion thereof) of the mammalian glycosyltransferase. In such a case, the resulting hybrid enzyme would have the amino-terminal cytoplasmic tail of the plant glycosyltransferase linked to the plant glycosyltransferase transmembrane domain linked to the stem region of the plant glycosyltransferase in the normal manner of the wild-type plant enzyme – but the stem region would be linked to the catalytic domain of the mammalian glycosyltransferase (or portion thereof).

In the above discussion, the use of the phrase "or portion thereof" was used to expressly indicate that less than the entire region/domain might be employed in the particular case (*e.g.*, a fragment might be used). For example, the cytoplasmic tail of glycosyltransferases ranges from

approximately 5 to 50 amino acids in length, and more typically 15 to 30 amino acids, depending on the particular transferase. A "portion" of the cytoplasmic tail region is herein defined as no fewer than four amino acids and can be as large as up to the full length of the region/domain less one amino acid. It is desired that the portion function in a manner analogous to the full length region/domain – but need not function to the same degree. For example, to the extent the full-length cytoplasmic tail functions as a Golgi retention region or ER retention signal, it is desired that the portion employed in the above-named embodiments also function as a Golgi or ER retention region, albeit perhaps not as efficiently as the full-length region.

Similarly, the transmembrane domain is typically 15-25 amino acids in length and made up of primarily hydrophobic amino acids. A "portion" of the transmembrane domain is herein defined as no fewer than ten amino acids and can be as large as up to the full length of the region/domain (for the particular type of transferase) less one amino acid. It is desired that the portion function in a manner analogous to the full length region/domain – but need not function to the same degree. For example, to the extent the full-length transmembrane domain functions as the primary Golgi retention region or ER retention signal, it is desired that the portion employed in the above-named embodiments also function as a Golgi or ER retention region, albeit perhaps not as efficiently as the full-length region. The present invention specifically contemplates conservative substitutions to create variants of the wild-type transmembrane domain or portions thereof. For example, the present invention contemplates replacing one or more hydrophobic amino acids (shown as "H" in the schematic above) of the wild-type sequence with one or more different amino acids, preferably also hydrophobic amino acids.

A portion of the catalytic domain can be as large as the full length of the domain less on amino acid. Where the catalytic domain is from a beta1,4-galactosyltransferase, it is preferred that the portion include at a minimum residues 345-365 which are believed to be involved in the conformation conferring an oligosaccharide acceptor binding site (it is preferred that the portion include this region at a minimum and five to ten amino acids on either side to permit the proper conformation).

The present invention also includes synthetic CTS regions and portions thereof. A "portion" of a CTS region must include at least one (and may include more than one) entire domain (*e.g.*, the entire transmembrane domain) but less than the entire CTS region.

Importantly, by using the term "CTS region" or "transmembrane domain" it is not intended that only wild type sequences be encompassed. Indeed, this invention is not limited to natural glycosyltransferases and enzymes involved in glycosylation, but also includes the use of synthetic enzymes exhibit the same or similar function. In one embodiment, wild type domains are changed (e.g. by deletion, insertion, replacement and the like).

Finally, by using the indicator "Tm" when referring to a particular hybrid (*e.g.*, "TmXyl-), entire transmembrane/CTS domains (with or without changes to the wild-type sequence) as well as portions (with or without changes to the wild-type sequence) are intended to be encompassed.

SUMMARY OF THE INVENTION

The present invention contemplates nucleic acid (whether DNA or RNA) encoding hybrid enzymes (or "fusion proteins"), vectors containing such nucleic acid, host cells (including but not limited to cells in plant tissue and whole plants) containing such vectors an expressing the hybrid enzymes, and the isolated hybrid enzyme(s) themselves. In one embodiment, expression of said hybrid enzymes (or "fusion proteins") results in changes in glycosylation, such as, but not limited to, reduction of sugar moieties such as xylose, fucose, Lewis$^{A/B/X}$ or other sugar structures that interfere with desired glycoform accumulation. In one embodiment, the present invention contemplates nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising a CTS region (or portion thereof) of a glycosyltransferase (including but not limited to a plant glycosyltransferase) and a catalytic region (or portion thereof) of a non-plant glycosyltransferase (e.g., mammalian, fish, amphibian, fungal). It is preferred that, when expressed, the CTS region (or portion thereof) is linked (directly or indirectly) in operable combination to said catalytic region (or portion thereof). The linking is preferably covalent and the combination is operable in that the catalytic region exhibits catalytic function (even if said catalytic function is reduced as compared to the wild-type enzyme). The linking can be direct in the sense that there are no intervening amino acids or other regions/domains. On the other hand, the linking can be indirect in that there are intervening amino acids (or other chemical groups) and/or other regions/domains between them. Of course, the nucleic acid used to make the nucleic acid encoding the above-described hybrid enzyme(s) can be obtained enzymatically from a physical sequence (e.g. genomic DNA, a cDNA, and the like) or alternatively, made synthetically using a reference sequence (e.g. electronic or hardcopy sequence) as a guide.

In a particular embodiment, the present invention contemplates nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising a transmembrane region (*e.g.*, at least a transmembrane region and optionally more of the CTS region) of a plant glycosyltransferase and a catalytic region (or portion thereof) of a non-plant (such as a mammalian) glycosyltransferase. Again, it is preferred that, when expressed, these regions are linked (directly or indirectly) in operable combination. In yet another embodiment, the present invention contemplates nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising a transmembrane domain (or portion thereof) of a plant glycosyltransferase and a catalytic region (or portion thereof) of a mammalian glycosyltransferase. Again, it is preferred that, when expressed, these regions are linked (directly or indirectly) in operable combination.

It is not intended that the present invention be limited to particular transferases. In one embodiment, the plant glycosyltransferase is a xylosyltransferase. In another embodiment, the plant glycosyltransferase is a N-acetylglucosaminyltransferase. In another embodiment, the plant glycosyltransferase is a fucosyltransferase. In a preferred embodiment, the mammalian glycosyltransferase is a human galactosyltransferase (such as the human beta 1,4-

galactosyltransferase encoded by SEQ ID NO:1 wherein the nucleotides encoding the transmembrane domain are deleted and replaced).

It is not intended that the present invention is limited to the use of a plant-derived glycosyltransferase CTS-domain and a human glycosyltransferase catalytic domain but also vice versa and the use of any CTS-domain of a glycosyltransferase in combination with the catalytic fragment of at least one other glycosyltransferase. Indeed, the present invention broadly contemplates, in one embodiment, nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising a transmembrane region of a first glycosyltransferase and a catalytic region of a second glycosyltransferase. It is preferred that said first and second glycosyltransferases are from different species (and can be from a different genus or even from a different phylum). In one embodiment, said first glycosyltransferase comprises a plant glycosyltransferase. In another embodiment, said plant glycosyltransferase is a xylosyltransferase. In yet another embodiment, said plant glycosyltransferase is a fucosyltransferase. In a preferred embodiment said second glycosyltransferase comprises a mammalian glycosyltransferase. In a particularly preferred embodiment, said mammalian glycosyltransferase is a human galactosyltransferase.

It is not intended that the present invention be limited to circumstances where the first and second glycosyltransferases are plant and non-plant, respectively. In one embodiment, said first glycosyltransferase comprises a first mammalian glycosyltransferase and said second glycosyltransferase comprises a second mammalian glycosyltransferase. In a preferred embodiment, said first mammalian glycosyltransferase is a non-human glycosyltransferase and said second mammalian glycosyltransferase is a human glycosyltransferase.

It is not intended that the present invention be limited to the type of vector. In one embodiment, the present invention contemplates an expression vector, comprising the nucleic acid encoding the above-described hybrid enzyme.

It is also not intended that the present invention be limited to the type of host cells. A variety of prokaryotic and eukaryotic host cells are commercially available for expressing proteins. In one embodiment, the present invention contemplates a host cell containing the vector comprising the nucleic acid encoding the above-described hybrid enzyme (with or without other vectors or other nucleic acid encoding other hybrid enzymes or glycosyltransferases). In a preferred embodiment, the host cell is a plant cell. In a particularly preferred embodiment, the present invention contemplates a plant comprising such a host cell.

It is not intended that the present invention be limited by the method by which host cells are made to express the hybrid enzymes of the present invention. In one embodiment, the present invention contemplates a method, comprising: a) providing: i) a host cell (such as a plant cell, whether in culture or as part of plant tissue or even as part of an intact growing plant), and ii) an expression vector comprising nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising at least a portion of a CTS region of a plant glycosyltransferase (*e.g.* the transmembrane domain) and at least a portion of a catalytic region of a mammalian glycosyltransferase; and b)

introducing said expression vector into said plant cell under conditions such that said hybrid enzyme is expressed. Again, it is not intended that the present invention be limited to particular transferases. In one embodiment, the plant glycosyltransferase used in the above-described method is a xylosyltransferase. In another embodiment, the plant glycosyltransferase is a N-acetylglucosaminyltransferase. In another embodiment, the plant glycosyltransferase is a fucosyltransferase. In a preferred embodiment, the mammalian glycosyltransferase used in the above-described method is a human galactosyltransferase (such as the human beta 1,4-galactosyltransferase encoded by SEQ ID NO:1 wherein the nucleotides encoding the transmembrane domain are deleted and replaced) (or simply where the nucleotides of SEQ ID NO:1 encoding the catalytic domain, or portion thereof, are taken and linked to nucleotides encoding the CTS region, or portion thereof, of a plant glycosyltransferase.).

It is not intended that the present invention be limited to a particular scheme for controlling glycosylation of a heterologous protein using the hybrid enzymes described above. In one embodiment, the present invention contemplates a method, comprising: a) providing: i) a host cell (such as a plant cell), ii) a first expression vector comprising nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising at least a portion of a CTS region (*e.g.* at least a transmembrane domain) of a first (such as a plant) glycosyltransferase and at least a portion of a catalytic region of a second (such as a mammalian) glycosyltransferase, and iii) a second expression vector comprising nucleic acid encoding a heterologous glycoprotein; (or portion thereof; and b) introducing said first and second expression vectors into said plant cell under conditions such that said hybrid enzyme and said heterologous protein are expressed. Alternatively, a single vector with nucleic acid encoding both the hybrid enzyme (or hybrid enzymes) and the heterologous glycoprotein might be used. Regardless of which method is used, the invention contemplates, in one embodiment, the additional step (c) of isolating the heterologous protein – as well as the isolated protein itself as a composition.

On the other hand, the present invention also contemplates introducing different vectors into different plant cells (whether they are cells in culture, part of plant tissue, or even part of an intact growing plant). In one embodiment, the present invention contemplates a method, comprising: a) providing: i) a first plant comprising a first expression vector, said first vector comprising nucleic acid encoding a hybrid enzyme (or encoding two or more hybrid enzymes), said hybrid enzyme comprising at least a portion of a CTS region (*e.g.* the first approximately 40-60 amino acids of the N-terminus) of a plant glycosyltransferase and at least a portion of a catalytic region of a mammalian glycosyltransferase, and ii) a second plant comprising a second expression vector, said second vector comprising nucleic acid encoding a heterologous protein (or portion thereof); and crossing said first plant and said second plant to produce progeny expressing said hybrid enzyme and said heterologous protein. Of course, such progeny can be isolated, grown up, and analyzed for the presence of each (or both) of the proteins. Indeed, the heterologous protein can be used (typically first purified substantially free of plant cellular material) therapeutically (*e.g.*, administered to a human or animal,

whether orally, by intravenous, transdermally or by some other route of administration) to treat or prevent disease.

It is not intended that the present invention be limited to a particular heterologous protein. In one embodiment, any peptide or protein that is not endogenous to the host cell (or organism) is contemplated. In one embodiment, the heterologous protein is an antibody or antibody fragment. In a particularly preferred embodiment, the antibody is a human antibody or "humanized" antibody expressed in a plant in high yield. "Humanized" antibodies are typically prepared from non-human antibodies (*e.g.* rodent antibodies) by taking the hypervariable regions (the so-called CDRs) of the non-human antibodies and "grafting" them on to human frameworks. The entire process can be synthetic (provided that the sequences are known) and frameworks can be selected from a database of common human frameworks. Many times, there is a loss of affinity in the process unless either the framework sequences are modified or the CDRs are modified. Indeed, increases in affinity can be revealed when the CDRs are systematically mutated (for example, by randomization procedures) and tested.

While the present invention is particularly useful in the context of heterologous proteins, in one embodiment, the hybrid enzymes of the present invention are used to change the glycosylation of endogenous proteins, *i.e.* proteins normally expressed by the host cell or organism.

The present invention specifically contemplates the plants themselves. In one embodiment, the present invention contemplates a plant, comprising first and second expression vectors, said first vector comprising nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising at least a portion of a CTS region (*e.g.* the cytoplasmic tail together with at least a portion of the transmembrane domain) of a plant glycosyltransferase and at least a portion of a catalytic region of a mammalian glycosyltransferase, said second expression vector, said second vector comprising nucleic acid encoding a heterologous protein (or portion thereof). In a preferred embodiment, by virtue of being expressed along with the hybrid enzyme (or hybrid enzymes) of the present invention, the heterologous protein displays reduced (10% to 99%) alpha 1,3 -fucosylation (or even no fucosylation), as compared to when the heterologous protein is expressed in the plant in the absence of the hybrid enzyme (or enzymes). In a preferred embodiment, by virtue of being expressed along with the hybrid enzyme (or hybrid enzymes) of the present invention, the heterologous protein displays reduced (10% to 99%) xylosylation (or even no xylose), as compared to when the heterologous protein is expressed in the plant in the absence of the hybrid enzyme (or enzymes). In a preferred embodiment, by virtue of being expressed along with the hybrid enzyme (or hybrid enzymes) of the present invention, the heterologous protein displays both reduced fucose and xylose, as compared to when the heterologous protein is expressed in the plant in the absence of the hybrid enzyme (or enzymes).

It is not intended that the present invention be limited to a particular theory by which reduced fucose and/or xylose is achieved. Very little is known about the sub-Golgi sorting mechanism in plants. The mammalian specific β(1,4)-galactosyltransferase (GalT) has been used (see the

Examples below) as an excellent first marker to study this phenomenon since it generates glycan structures not normally found in plants. The glycan structures of plants that express galactosyltransferase has been compared with glycan structures from plants that express a chimeric galactosyltransferase of which the CTS domain is exchanged for that of a plant xylosyltransferase (or portion thereof). The change in observed glycan structures show that the galactosyltransferase is, as in mammals, confined to a specific sub-compartment of the plant Golgi. Without limiting the invention to any particular mechanism, the sorting mechanism of plants and mammals are apparently conserved even to the extent that glycosyltransferases unknown to plants are routed to specific analogous location in the Golgi. This location is later in the Golgi than where the endogenous xylosyl-, fucosyl- and GlcNAcTII (GnTII) transferases are located.

The finding that N-glycans in these plants that express relocalised variants of GalT containing significantly less xylose and fucose is also of biotechnological relevance. For glycoproteins intended for therapeutic use in mammals, such as humans, the approach of certain embodiments of the present invention provides methods and compositions for controlling N-linked glycosylation of glycoproteins in plants so that glycoprotein essentially free of xylose and fucose and containing at least a bi-antennary N-glycans (but not limited to bi-antennary, also include tri-antennary, and the like) and (at least one) galactose residue on at least one of the arms of the N-glycan can be obtained. Hence, it is not intended that the present invention is limited to bi-antennary N-glycans but also includes bisected bi-antennary N-glycans, tri-antennary N-glycans, and the like. Furthermore, the invention is not limited to complex–type N-glycans but also includes hybrid-type N-glycans and other type N-glycans. The present invention contemplates such resulting glyco-proteins. In addition, the methods and compositions of the present invention may be applicable for plants and non-plant systems where besides xylose, fucose, Lewis$^{A/B/X}$ type N-glycan modifications (β1-3-GalT, α1-4-FucT, other) or other sugars, "interfere" with desired glycoform accumulation.

In one embodiment, the invention is directed to controlling N-linked glycosylation of plants by modulating the localization of enzymes involved in glycan biosynthesis in the Golgi apparatus. Specifically, embodiments of the invention are directed to a method of producing in a plant host system a glycoprotein having bi-antennary glycans and containing at least one galactose residues on at least one of the arms and which are devoid (or reduced in) of xylose and fucose, comprising:(a) preventing (or inhibiting) addition of xylose and fucose on the core of the glycan of said glycoprotein and (b) adding one or preferably two galactose residues to said arms.

Addition of xylose and fucose to said heterologous glycoprotein may be reduced or even prevented by introducing to said plant host system a nucleic acid encoding a hybrid enzyme comprising a CTS region (or portion thereof) of a protein, particularly an enzyme such as plant xylosyltransferase and catalytic region (or portion thereof) of a galactosyltransferase not normally found in a plant, or a modified galactosyltransferase where its transmembrane portion has been removed and endoplasmic reticulum retention signal have been inserted, wherein said protein or enzyme acts earlier in the Golgi apparatus of a plant cell in said plant host system than said

galactosyltransferase. It is preferred that the galactosyltransferase is a mammalian galactosyltransferase and in particular, a human galactosyltransferase. In a most specific embodiment, said galactosyltransferase is human β1,4 galactosyltransferase (GalT). In a preferred embodiment, said xylosyltransferase is a β1,2-xylosyltransferase. The exchange of the CTS region or CTS fragment of a mammalian glycosyltransferase (such as a galactosyltransferase) by one from the group of enzymes that act earlier in the Golgi apparatus than galactosyltransferase including but not limited to those from of XylT, FucT, GnTI, GnTII, GnTIII, GnTIV, GnTV, GnTVI, ManI, ManII and ManIII results in strongly reduced amounts of glycans that contain the undesired xylose and fucose residues (see Figure 2). In addition, galactosylation is improved and the diversity in glycans is reduced. While not limited to any particular mechanism, the increase in galactosylated glycans that carry neither xylose nor fucose is believed to be mainly attributed to the accumulation of GalGNMan5, GNMan5 or GalGNMan4. Also, galactosylation occurs on one glycan arm only. Apparently, the galactosylation earlier in the Golgi inhibits trimming of the said glycoforms by Mannosidase II (ManII) to GalGNMan3. Also addition of the second GlcNAc by GlcNAcTII (GnTII) is inhibited.

Therefore, in one embodiment, a further step is contemplated to obtain the desired glycoprotein that has both arms galactosylated and yet is essentially devoid of xylose and fucose. Thus, in one embodiment, the method of the invention as noted above further comprises adding galactose residues to the arms of said glycoprotein (see Figure 3). In one embodiment of the invention, galactose residues are added onto both arms by introducing to said plant host system (a) a nucleic acid sequence encoding a first hybrid enzyme comprising the CTS region (or fragment, such as one including the transmembrane domain) of GnTI and the active domain (or portion thereof) of GnTII; (b) a nucleic acid sequence encoding the second hybrid enzyme comprising the CTS region (or fragment, such as one including the transmembrane of GnTI and the active domain of ManII and (c) a nucleic acid sequence encoding a third hybrid enzyme comprising the CTS region (or fragment, such as one including the transmembrane domain) of XylT and the active domain (or portion thereof) of human galactosyltransferse (TmXyl-GalT). In another embodiment of the invention, galactose residues are added onto both arms by introducing to said plant host system (a) a nucleic acid sequence encoding a first hybrid enzyme comprising the CTS region (or fragment, such as one including the transmembrane domain) of ManI and the active domain (or portion thereof) of GnTI; (b) a nucleic acid sequence encoding the second hybrid enzyme comprising the CTS region (or fragment, such as one including the transmembrane domain) of ManI and the active domain (or portion thereof) of GnTII; (c) a nucleic acid sequence encoding the third hybrid enzyme comprising the CTS region (or fragment, such as one including the transmembrane domain) of ManI and the active domain (or portion thereof) of ManII, and (d) a nucleic acid sequence encoding a fourth hybrid enzyme comprising the CTS region (or fragment, such as one including the transmembrane domain) of XylT and the active domain (or portion thereof) of human galactosyltransferse (TmXyl-GalT).

It is not intended that the present invention be limited to particular combinations of hybrid enzymes or the number of such hybrid enzymes employed in a single cell, plant tissue or plant. In a preferred embodiment, the present invention contemplates host cells expressing TmXyl-GalT plus TmGnTI-GnTII plus TmGnTI-ManII. In one embodiment of the invention, galactose residues are added to said arms by introducing to said plant host system (a) a nucleic acid sequence encoding a first hybrid enzyme comprising a CTS region (or fragment thereof) of a protein, particularly an enzyme, including but not limited to N-acetylglucosaminyltransferase I (GnTI) and a catalytic region (or portion thereof) of a mannosidase II (ManII), wherein said enzyme acts earlier in the Golgi apparatus of a plant cell in said plant host system than said mannosidase II or modified mannosidase II where its transmembrane portion has been deleted and endoplasmic reticulum retention signal have been inserted and (b) a nucleic acid sequence encoding a second hybrid enzyme comprising a CTS region (or fragment, such as one including the transmembrane domain) of an enzyme including but not limited to N-acetyl-glucosaminyltransferase I (GnTI) and a catalytic region (or portion thereof) of a N-acetylglucosaminyl-transferase II (GnTII), wherein said enzyme acts earlier in the Golgi apparatus of a plant cell in said plant host system than said N acetylglucosaminyl-transferaseII (GnTII) or modified N-acetylglucosaminyltransferase II (GnTII) where its transmembrane portion has been deleted and an endoplasmic reticulum retention signal have been inserted. The sequences encoding N-acetylglucosaminyltransferases or mannosidase II or the said transmembrane fragments can originate form plants or from eukaryotic non-plant organisms (*e.g.*, mammals).

In yet another preferred embodiment, the present invention contemplates a host cell expressing TmXyl-GalT plus TmManI-GnTI plus TmManI-ManII plus TmManI-GnTII. In another embodiment of the invention, galactose residues are added to said arms by introducing to said plant host system (a) a nucleic acid sequence encoding a first hybrid enzyme comprising a CTS region (or fragment, such as one including the transmembrane domain) of a protein, particularly an enzyme, including but not limited to Mannosidase I (ManI) and a catalytic region (or portion thereof) of a N acetylglucosaminyltransferase I (GnTI), wherein said enzyme acts earlier in the Golgi apparatus of a plant cell in said plant host system than said N-acetylglucosaminyl-transferase I (GnTI) or modified N acetylglucosaminyltransferase I (GnTI) where its transmembrane portion has been deleted and endoplasmic reticulum retention signal have been inserted and (b) a nucleic acid sequence encoding a second hybrid enzyme comprising a CTS region (or fragment, such as one including the transmembrane domain) of an enzyme including but not limited to Mannosidase I (ManI) and a catalytic region (or portion thereof) of a Mannosidase II (ManII), wherein said enzyme acts earlier in the Golgi apparatus of a plant cell in said plant host system than said Mannosidase II (ManII) or modified Mannosidase II (ManII) where its transmembrane portion has been deleted and an endoplasmic reticulum retention signal have been inserted and (c) a nucleic acid sequence encoding a third hybrid enzyme comprising a CTS region (or fragment, such as one including the transmembrane domain) of an enzyme including but not limited to Mannosidase I (ManI) and a catalytic region (or portion thereof) of a N-acetylglucos-aminyltransferase II (GnTII), wherein said

enzyme acts earlier in the Golgi apparatus of a plant cell in said plant host system than said N-acetylglucosaminyltransferase II (GnTII) or modified N-acetylglucosaminyltransferase II (GnTII) where its transmembrane portion has been deleted and an endoplasmic reticulum retention signal have been inserted. The sequences encoding N-acetylglucosaminyltransferases or mannosidases or the said transmembrane fragments can originate from plants or from eukaryotic non-plant organisms (*e.g.*, mammals).

In still another preferred embodiment, the present invention contemplates host cells expressing TmXyl-GalT plus ManIII. In another embodiment of the invention, galactose residues are added to said arms by introducing to said plant host system (a) a nucleic acid sequence encoding a Mannosidase III (ManIII, wildtype gene sequence but not limited to: also ManIII with endoplasmic reticulum retention signal; ManIII with transmembrane fragment of early (cis-) Golgi apparatus glycosyltransferase (GnTI, ManI, GnTIII). The sequences encoding Mannosidase III can originate form insects, preferably from *Spodoptera frugiperda* or *Drosophila melanogaster* (but not limited to), human or from other organisms.

In still another preferred embodiment, the present invention contemplates a host cell expressing TmXyl-GalT plus ManIII plus TmGnTI-GnTII. In yet another preferred embodiment, the present invention contemplates a host cell expressing TmXyl-GalT plus ManIII plus TmManI-GnTI plus TmManI-GnTII.

The method of the invention may optionally comprise, in one embodiment, introducing into said plant host system a mammalian N-acetylglucosaminyltransferase GnTIII, particularly a human GnTIII or hybrid protein comprising a catalytic portion of mammalian GnTIII and a transmembrane portion of a protein, said protein residing in the ER or earlier compartment of the Golgi apparatus of a eukaryotic cell. For example, in one embodiment, the hybrid enzyme TmXyl-GnTIII is contemplated (along with nucleic acid coding for such a hybrid enzyme, vectors containing such nucleic acid, host cells containing such vectors, and plants – or plant parts – containing such host cells). In another embodiment, the hybrid enzyme TmFuc-GnTIII is contemplated (along with nucleic acid coding for such a hybrid enzyme, vectors containing such nucleic acid, host cells containing such vectors, and plants – or plant parts – containing such host cells). The present invention specifically contemplates host cells expressing such hybrid enzymes (with or without additional hybrid enzymes or other glycosyltransferases).

The invention is further directed to said hybrid and modified enzymes, nucleic acid sequences encoding said hybrid enzymes, vectors comprising said nucleic acid sequences and methods for obtaining said hybrid enzymes. Furthermore, the invention is directed to a plant host system comprising a heterologous glycoprotein having preferably complex type bi-antennary glycans and containing at least one galactose residue on at least one of the arms and are devoid of xylose and fucose. A "heterologous glycoprotein" is a glycoprotein originating from a species other than the

plant host system. The glycoprotein may include but is not limited to antibodies, hormones, growth factors and growth factor receptors and antigens.

Indeed, the present invention is particularly useful for controlling the glycosylation of heterologous glycoproteins, such as antibodies or antibody fragments (single chain antibodies, Fab fragments, Fab_2 fragments, Fv fragments, and the like). To control the glycosylation of an antibody, the gene construct encoding a hybrid enzyme of the present invention (*e.g.*, the TmXyl-GalT gene construct) can be introduced in transgenic plants expressing an antibody (*e.g.*, monoclonal antibody) or antibody fragment. On the other hand, the gene(s) encoding the antibody (or antibody fragment) can be introduced by retransformation of plant expressing TmXyl-GalT gene construct. In still another embodiment, the binary vector harbouring the TmXyl-GalT expression cassette can be co-transformed to plants together with a plant binary vector harbouring the expression cassettes comprising both light and heavy chain sequences of a monoclonal antibody on a single T-DNA or with binary vectors harbouring the expression cassettes for light and heavy chain sequences both separately on independent T-DNA's but both encoding a monoclonal antibody. The present invention specifically contemplates, in one embodiment, crossing plants expressing antibodies with plant expressing the hybrid glycosyltransferase(s) of the present invention.

A "host system" may include but is not limited to any organism containing glycoproteins with N-glycans.

A "plant host system" may include but is not limited to a plant or portion thereof, which includes but is not limited to a plant cell, plant organ and/or plant tissue. The plant may be a monocotyledon (monocot) which is a flowering plant whose embryos have one cotyledon or seed leaf and includes but is not limited to lilies, grasses, corn (*Zea mays*), rice, grains including oats, wheat and barley, orchids, irises, onions and palms. Alternatively, the plant may be a dicotyledenon (dicot) which includes but is not limited to tobacco (*Nicotiana)*, tomatoes, potatoes, legumes (e.g, alfalfa and soybeans), roses, daises, cacti, violets and duckweed. The plant may also be a moss which includes but is not limited to *Physcomitrella patens.*

The invention is further directed to a method for obtaining said plant host system. The method comprises crossing a plant expressing a heterologous glycoprotein with a plant comprising (a) a hybrid enzyme comprising a catalytic region (or portion thereof) of a galactosyltransferase not normally found in a plant and a CTS region (or fragment, such as one including the transmembrane domain) of a protein, wherein said protein acts earlier in the Golgi apparatus of a plant cell in said plant host system than said galactosyltransferase or a modified galactosyltransferase where its transmembrane portion has been deleted and endoplasmic reticulum retention signal has been inserted; (b) a hybrid enzyme comprising a CTS region (or portion thereof, such as one including the transmembrane domain) of a protein, particularly an enzyme, including but not limited to N-acetylglucosaminyltransferase I (GnTI) and a catalytic region (or portion thereof) of a mannosidase II (ManII), wherein said enzyme acts earlier in the Golgi apparatus of a plant cell in said plant host system than said mannosidase II or modified mannosidase II where its transmembrane

portion has been deleted and endoplasmic reticulum retention signal have been inserted and (c) a hybrid enzyme comprising at least a transmembrane region of an enzyme (such as the first 40-60 amino acids of the N-terminus) of a glycosyltransferase including but not limited to N-acetylglucosaminyltransferase I (GnTI) and a catalytic region of a N-acetylglucos-aminyltransferase II (GnTII), wherein said enzyme acts earlier in the Golgi apparatus of a plant cell in said plant host system than said N acetylglucosaminyltransferase II (GnTII) or modified N-acetylglucosaminyl-transferase II (GnTII) where its transmembrane portion has been deleted and an endoplasmic reticulum retention signal have been inserted., harvesting progeny from said crossing and selecting a desired progeny plant expressing said heterologous glycoprotein.

The invention is further directed to said plant or portion thereof which would constitute a plant host system. Said plant host system may further comprise a mammalian GnTIII enzyme or hybrid protein comprising a catalytic portion of mammalian GnTIII and a transmembrane portion of a protein, said protein residing in the ER or earlier compartment of the Golgi apparatus of a eukaryotic cell.

Additionally, the invention also provides the use of a plant host system to produce a desired glycoprotein or functional fragment thereof. The invention additionally provides a method for obtaining a desired glycoprotein or functional fragment thereof comprising cultivating a plant according to the invention until said plant has reached a harvestable stage, for example when sufficient biomass has grown to allow profitable harvesting, followed by harvesting said plant with established techniques known in the art and fractionating said plant with established techniques known in the art to obtain fractionated plant material and at least partly isolating said glycoprotein from said fractionated plant material.

Alternatively, said plant host cell system comprising said heterologous glycoprotein may also be obtained by introducing into a plant host cell system or portion thereof (a) a nucleic acid sequence encoding a hybrid enzyme comprising a catalytic region of a galactosyltransferase not normally found in a plant and at least the transmembrane region (or more of the CTS) of a protein, wherein said protein acts earlier in the Golgi apparatus of a plant cell in said plant host system than said galactosyltransferase or a modified galactosyltransferase where its transmembrane portion has been deleted and endoplasmic reticulum retention signal have been inserted; (b) a nucleic acid sequence encoding a first hybrid enzyme comprising at least the transmembrane region (or more of the CTS if desired) of a protein, particularly an enzyme, including but not limited to N-acetylglucosaminyltransferase I (GnTI) and a catalytic region of a mannosidase II (ManII) , wherein said enzyme acts earlier in the Golgi apparatus of a plant cell in said plant host system than said mannosidase II, or modified mannosidase II where its transmembrane portion has been deleted and endoplasmic reticulum retention signal have been inserted and (c) a nucleic acid sequence encoding a second hybrid enzyme comprising at least a transmembrane region (more of the CTS if desired) of an enzyme including but not limited to N-acetylglucosaminyl-transferase I (GnTI) and a catalytic region of a N-acetylglucosaminyltransferase II (GnTII), wherein said enzyme acts earlier in the

Golgi apparatus of a plant cell in said plant host system than said N- acetylglucos-aminyltransferase-II (GnTII) or modified N-acetylglucosaminyltransferase II (GnTII) where its transmembrane portion has been deleted and an endoplasmic reticulum retention signal have been inserted. and isolating a plant or portion thereof expressing said heterologous glycoprotein (or portion thereof). In one embodiment, one vector comprising all of the nucleic acid sequences is introduced into said plant host system. In another embodiment, each nucleic acid sequence is inserted into separate vectors and these vectors are introduced into said plant host system. In another embodiment combinations of two or more nucleic acid sequences are inserted into separate vectors which are than combined into said plant host system by retransformation or co-transformation or by crossing.

The invention also provides use of such a plant-derived glycoprotein or functional fragment thereof according to the invention for the production of a composition, particularly, pharmaceutical composition, for example for the treatment of a patient with an antibody, a hormone, a vaccine antigen, an enzyme, or the like. Such a pharmaceutical composition comprising a glycoprotein or functional fragment thereof is now also provided.

Finally, it is contemplated that the above-described approach may be useful in reducing the overall diversity in glycans in plants expressing one or more of the hybrid enzymes of the present invention (as compared to wild-type plants or plants simply transformed with only mammalian GalT).

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 compares the glycosylation pathway of glycoproteins in plants and in mammals.

Figure 2 shows the effect of exchanging the CTS fragment of galactosyltransferase with xylosyltransferase

Figure 3 shows the further effect of relocalizing mannosidase II and GlcNAcTII.

Figure 4 top panel shows a T-DNA construct carrying the genes encoding glycan modifying enzymes to produce efficiently galactosylated glycans that are devoid of immunogenic xylose and fucose and the bottom panel shows a T-DNA construct carrying antibody light chain and heavy chain genes.

Figure 5 shows the nucleic acid sequence (SEQ ID NO:1) for a human galactosyltransferase (human B1,4-galactosyltransferase – GalT).

Figure 6 shows the nucleic acid sequence of Figure 5 along with the corresponding amino acid sequence (SEQ ID NO:2).

Figure 7 shows an illustrative mutated sequence (SEQ ID NO:59) derived the wild type amino acid sequence (SEQ ID NO:2) for a human galactosyltransferase, wherein a serine has been deleted from the cytoplasmic tail and a G-I-Y motif has been repeated. Of course, such changes are merely illustrative of the many possible changes within the scope of the present invention. For example, in one embodiment, the present invention contemplates mutated sequences wherein only deletions (one or more) are employed (*e.g.* deletions in the cytoplasmic tail domain or the stem

domain) – with no insertions or repeats. Similarly, in one embodiment, the present invention contemplates mutated sequences wherein only (one or more) insertions or replacements (*e.g.* in the transmembrane domain) are employed – with no deletions.

Figure 8 shows the nucleic acid sequence (SEQ ID NO:3) encoding a hybrid enzyme comprising human galactosyltransferase (human B1,4-galactosyltransferase – GalT). The upper case letters are nucleotides of *Arabidopsis thaliana* mRNA for beta 1,2-xylosyltransferase (database entry: EMBL:ATH277603, the TmXyl-fragment used involves nucleotides 135-297 of this database sequence).

Figure 9 shows the nucleic acid sequence of Figure 8 along with the corresponding amino acid sequence (SEQ ID NO:4).

Figure 10 shows the amino acid sequence (SEQ ID NO:4) for the hybrid enzyme encoded by the nucleic acid shown in Figure 8.

Figure 11 shows the nucleic acid sequence (SEQ ID NO:5) for the human glycosyltransferase GnTIII (along with additional sequence encoding a myc-tag) (primary accession number Q09327 GNT3 HUMAN).

Figure 12 shows the nucleic acid sequence of Figure 11 along with the corresponding amino acid sequence (SEQ ID NO:6).

Figure 13 shows the amino acid sequence (SEQ ID NO:6) for a human GnTIII (along with additional amino acid sequence of the myc epitope tag SEQ ID NO:7).

Figure 14 shows the nucleic acid sequence (SEQ ID NO:9) encoding one embodiment of a hybrid enzyme of the present invention, said hybrid enzyme comprising the transmembrane domain of a plant xylosyltransferase (TmXyl-) and the catalytic domain (along with other regions) for human GnTIII (TmXyl-GnTIII) (along with additional sequence encoding a myc-tag).

Figure 15 shows the nucleic acid sequence of Figure 14 along with the corresponding amino acid sequence (SEQ ID NO:10).

Figure 16 shows the amino acid sequence (SEQ ID NO:10) for hybrid enzyme encoded by the nucleic acid of Figure 14 (along with additional sequence for the myc epitope tag SEQ ID NO:7).

Figure 17 shows the complete nucleic acid sequence (SEQ ID NO:27) for a cassette encoding the hybrid enzymes TmXyl-GalT plus TmGnTI-GnTII plus TmGnTI-ManII).

Figure 18 shows the complete nucleic acid sequence (SEQ ID NO:28) for a cassette encoding the hybrid enzyme TmGnTI-ManII (with the RbcS1 promoter sequence SEQ ID NO:39 shown).

Figure 19 shows the nucleic acid sequence (SEQ ID NO:29) encoding the hybrid enzyme TmGnTI-ManII.

Figure 20 shows the nucleic acid sequence (SEQ ID NO:30) encoding the hybrid enzyme TmGnTI-GnTII.

Figure 21 shows the nucleic acid sequence (SEQ ID NO:31) encoding the hybrid enzyme TmGnTI-GnTII, wherein the transmembrane fragment used (designated TmGntI) has the nucleic acid sequence set forth in SEQ ID NO:32.

Figure 22A shows the nucleic acid sequence (SEQ ID NO:32) encoding one embodiment of a transmembrane domain fragment (TmGnTI). Figure 22B shows the nucleic acid sequence (SEQ ID NO:33) encoding another embodiment of a transmembrane domain fragment (TmManI).

Figure 23 shows the complete nucleic acid sequence (SEQ ID NO:34) for a triple cassette embodiment of the present invention.

Figure 24 shows the nucleic acid sequence (SEQ ID NO:35) for a hybrid gene expression cassette (TmManI-GnTI).

Figure 25 shows the nucleic acid sequence (SEQ ID NO:36) for the histone 3.1 promoter.

Figure 26 shows the nucleic acid sequence (SEQ ID NO:37) for the hybrid gene fusion (TmManI-TmGnTI).

Figure 27 shows the nucleic acid sequence (SEQ ID NO:38) for the hybrid gene fusion TmManI-ManII (with the RbcS1 promoter sequence SEQ ID NO:39 shown).

Figure 28 shows the nucleic acid sequence (SEQ ID NO:39) for the RbcS1 promoter.

Figure 29 shows the nucleic acid sequence (SEQ ID NO:40) for the hybrid gene TmManI-ManII wherein the nucleic acid sequence (SEQ ID NO:33) encoding the transmembrane fragment is shown.

Figure 30 shows the nucleic acid sequence (SEQ ID NO:41) for the hybrid gene TmManI-GnTII.

Figure 31 shows the nucleic acid sequence (SEQ ID NO:42) for the Lhca promoter.

Figure 32 shows the nucleic acid sequence (SEQ ID NO:43) for the hybrid gene TmManI-GnTII wherein the nucleic acid sequence (SEQ ID NO:33) encoding the transmembrane fragment is shown

Figure 33 shows the nucleic acid sequence (SEQ ID NO:44) for the terminator sequence used (see below).

Figure 34 is a Western Blot which examines total protein glycosylation of plants of the present invention compared to control plants.

Figure 35 is a lectin blot with RCA on F1 progeny of crossed plants, said progeny made according to one embodiment of the present invention

Figure 36 is a Western Blot. Panel A was assayed with anti-IgG antibody. Panel B was assayed with an anti-HRP antibody. Panel C was assayed with a specific anti-Xyl antibody fraction. Panel D was assayed with a specific anti-Fucose antibody fraction. Panel E was assayed with the lectin RCA.

Figure 37 shows the nucleic acid sequence (SEQ ID NO:49) of a hybrid gene wherein the aminoterminal CTS region of an insect Mannosidase III gene is replaced by a mouse signal peptide and a carboxyterminal endoplasmic reticulum retention signal (KDEL) was added.

Figure 38 shows the corresponding amino acid sequence (SEQ ID NO:50) for the nucleic acid sequence of Figure 37.

Figure 39 shows the nucleic acid sequence (SEQ ID NO:51) of a hybrid gene wherein the aminoterminal CTS region of a human beta-1,4-galactosyltransferase (GalT) gene is replaced by a mouse signal peptide and a carboxyterminal endoplasmic reticulum retention signal (KDEL) was added.

Figure 40 shows the corresponding amino acid sequence (SEQ ID NO:52) for the nucleic acid sequence of Figure 39.

Figure 41 shows the nucleic acid sequence (SEQ ID NO:53) of a hybrid gene wherein the aminoterminal CTS region of an *Arabidopsis thaliana* GnTI gene is replaced by a mouse signal peptide and a carboxyterminal endoplasmic reticulum retention signal (KDEL) was added.

Figure 42 shows the corresponding amino acid sequence (SEQ ID NO:54) for the nucleic acid sequence of Figure 41.

Figure 43 shows the nucleic acid sequence (SEQ ID NO:55) of a hybrid gene wherein the aminoterminal CTS region of an *Arabidopsis thaliana* GnTII gene is replaced by a mouse signal peptide and a carboxyterminal endoplasmic reticulum retention signal (KDEL) was added.

Figure 44 shows the corresponding amino acid sequence (SEQ ID NO:56) for the nucleic acid sequence of Figure 43.

Figure 45 shows the nucleic acid sequence (SEQ ID NO:57) of a hybrid gene wherein the aminoterminal CTS region of a human beta-1,4-galactosyltransferase (GalT) gene is replaced by the CTS region of the human gene for GnTI.

Figure 46 shows the corresponding amino acid sequence (SEQ ID NO:58) for the nucleic acid sequence of Figure 45.

Figure 47 is a schematic of how enzymes might be localized to the Golgi.

Figure 48 is a non-limiting speculative schematic of how the "swapping" of regions of transferases might cause relocalization.

DETAILED DESCRIPTION OF THE INVENTION

Hybrid Enzymes

The nucleic acid sequences encoding the various glycosylation enzymes such as mannosidases, GlcNAcTs, galactosyltransferases may be obtained using various recombinant DNA procedures known in the art, such as polymerase chain reaction (PCR) or screening of expression libraries to detect cloned DNA fragments with shared structural features. See, *e.g.*, Innis *et al.*, 1990, *PCR: A Guide to Methods and Application*, Academic Press, New York. Other nucleic acid amplification procedures such as ligase chain reaction (LCR), ligated activated transcription (LAT) and nucleic acid sequence-based amplification (NASBA) or long range PCR may be used.

Once the DNA fragments are generated, identification of the specific DNA fragment containing the desired gene may be accomplished in a number of ways. For example, if an amount of a portion of a gene or its specific RNA, or a fragment thereof, is available and can be purified and

labeled, the generated DNA fragments may be screened by nucleic acid hybridization to the labeled probe [Benton and Davis, *Science* 196:180 (1977); Grunstein and Hogness, *Proc. Natl. Acad. Sci. U.S.A.* 72:3961 (1975)]. Alternatively, the presence of the gene may be detected by assays based on the physical, chemical, or immunological properties of its expressed product. For example, cDNA clones, or DNA clones which hybrid-select the proper mRNAs, can be selected which produce a protein that, *e.g.*, has similar or identical electrophoretic migration, isoelectric focusing behavior, proteolytic digestion maps, or antigenic properties as known for the protein of interest.

A nucleic acid sequence encoding a hybrid enzyme comprising a transmembrane portion of a first enzyme and a catalytic portion of a second enzyme may be obtained as follows. The sequence encoding the transmembrane portion is removed from the second enzyme, leaving a nucleic acid sequence comprising a nucleic acid sequence encoding the C-terminal portion of the second enzyme, which encompasses the catalytic site. The sequence encoding the transmembrane portion of the first enzyme is isolated or obtained via PCR and ligated to the sequence encoding a sequence comprising the C-terminal portion of the second enzyme.

Modified Enzymes

A nucleic acid sequence encoding a protein, particularly enzymes such as galactosyltransferases, mannosidases and N-acetylglucosamine transferases that are retained in the ER may be obtained by removing the sequence encoding the transmembrane fragment and substituting it for a methionine (initiation of translation) codon and by inserting between the last codon and the stop codon of galactosyltransferase the nucleic acid sequence encoding an ER retention signal such as the sequence encoding KDEL (amino acid residue sequence: lysine-aspartic acid-glutamic acid-leucine) [Rothman *Cell* 50:521 (1987)].

Using Domains and Portions Thereof

As noted above, the phrases "at least a portion of" or a "fragment of" refers to the minimal amino acid sequence necessary for a protein or a peptide to retain its natural or native function. For example, the function of an enzyme could refer to its enzymatic or catalytic role, its ability to anchor a protein in the Golgi apparatus, or as a signal peptide. Thus, the phrases "at least a portion of a transmembrane domain" or "a fragment of a transmembrane domain" each refer to the smallest amino acid segment of a larger transmembrane domain that still retains at least part of the native transmembrane functionality (for example, the function may be evident, albeit decreased). As another example, the phrases "at least a portion of a catalytic region" or "a fragment of a catalytic region" each refer to the smallest amino acid segment of a larger catalytic region that still retains at least part of the native catalytic functionality (again, even if somewhat decreased). As discussed herein, one skilled in the art will know the minimal amino acid segment that is necessary for a protein or a peptide to retain at least some of the functionality of the native protein or peptide.

The glycosyltransferase enzymes are typically grouped into families based on the type of sugar they transfer (galactosyltransferases, sialyltransferases, etc.). Based on amino-acid sequence similarity and the stereochemical course of the reaction, glycosyltransferases can be classified into at least 27 and perhaps as many as 47 different families [Campbell *et al.*, *Biochem. J.* 326:929-939 (1997), *Biochem. J.* 329:719 (1998)]. The majority of glycosyltransferases cloned to date are type II transmembrane proteins (*i.e.*, single transmembrane domain with the NH_2 terminus in the cytosol and the COOH terminus in the lumen of the Golgi apparatus). Regardless of how they are classified, all glycosyltransferases share some common structural features: a short NH_2-terminal cytoplasmic tail, a 16-20 amino acid signal-anchor or transmembrane domain, and an extended stem region which is followed by the large COOH-terminal catalytic domain. The cytoplasmic tail appears to be involved in the specific localization of some types of glycosyltransferases to the Golgi [Milland *et al.*, *J. Biol. Chem.* 277:10374-10378]. The signal anchor domains can act as both uncleavable signal peptides and as membrane-spanning regions that orient the catalytic domains of the glycosyltransferases within the lumen of the Golgi apparatus.

In one embodiment of the present invention, a portion defined by the N-terminal 77 amino acids of *Nicotiana benthamiana* (tobacco) acetylglucosaminyltransferase I are contemplated for use in the hybrid enzyme(s), since this portion has been found to be sufficient to target to and to retain a reporter protein in the plant Golgi apparatus [Essl *et al.*, *FEBS Lett* 453:169-173 (1999)]. Subcellular localization in tobacco of various fusion proteins between the putative cytoplasmic, transmembrane and stem domains revealed that the cytoplasmic-transmembrane domains alone were sufficient to sustain Golgi retention of β 1,2-xylosyltransferase without the contribution of any luminal sequences [Dirnberger *et al.*, *Plant Mol. Biol.* 50:273-281 (2002)]. Thus, as noted above, certain embodiments of the present invention utilize portions of the CTS region which involve only the cytoplasmic-transmembrane domains (or portions thereof) without utilizing the stem region of the CTS region. However, while some types of glycosyltransferases rely primarily on their transmembrane domain for Golgi retention, other types require their transmembrane region and sequences flanking one or both sides of this region [Colley, *Glycobiology* 7:1-13 (1997)]. For example, the N-terminal peptide encompassing amino acids 1 to 32 appears to be the minimal targeting signal sufficient to localize β 1,6 N-acetylglucosaminyltransferase to the Golgi. This peptide makes up the cytoplasmic and transmembrane domains of this enzyme [Zerfaoui *et al.*, *Glycobiology* 12:15-24].

A great deal of information is available on the amino acid sequences of the domains for specific glycosyltransferases. For example, the amino acid sequence of the mammalian galactosyltransferase provided in GenBank Accession No. AAM17731 has the "stem" and "catalytic" domains spanning residues 19 to 147 and residues 148 to 397, respectively [U.S. Patent No. 6,416,988, hereby incorporated by reference] – and the present invention, in certain embodiments, specifically contemplates such portions for use in the hybrid enzyme(s). The amino acid sequence of the rat liver sialyltransferase provided in GenBank Accession No. AAC91156 has a

9-amino acid NH_2-terminal cytoplasmic tail, a 17-amino acid signal-anchor domain, and a luminal domain that includes an exposed stem region followed by a 41 kDa catalytic domain [Hudgin *et al.*, *Can. J. Biochem.* 49:829-837 (1971); U.S. Patent Nos. 5,032,519 and 5,776,772, hereby incorporated by reference]. Known human and mouse β 1,3-galactosyltransferases have a catalytic domain with eight conserved regions [Kolbinger *et al.*, *J. Biol. Chem.* 273:433-440 (1998); Hennet *et al.*, *J. Biol. Chem.* 273:58-65 (1998); U.S. Patent No. 5,955,282, hereby incorporated by reference]. For example, the amino acid sequence of mouse UDP-galactose: β-N-acetylglucosamine β 1,3-galactosyltransferase-I provided in GenBank Accession No. NM020026 has the following catalytic regions: region 1 from residues 78-83; region 2 from residues 93-102; region 3 from residues 116-119; region 4 from residues 147-158; region 5 from residues 172-183; region 6 from residues 203-206; region 7 from amino acid residues 236-246; and region 8 from residues 264-275. [Hennet *et al.*, supra.] – all of which are contemplated in certain embodiments of the present invention as useful portions in the context of the hybrid enzyme(s) discussed above.

While earlier comparisons amongst known cDNA clones of glycosyltransferases had revealed very little sequence homology between the enzymes [Paulson *et al.*, *J. Biol. Chem.* 264:17615-618 (1989)], more recent advances have made it possible to deduce conserved domain structures in glycosyltransferases of diverse specificity [Kapitonov *et al.*, *Glycobiology* 9:961-978 (1999)]. For example, the nucleic acid and amino acid sequences of a number of glycosyltransferases have been identified using sequence data provided by the complete genomic sequences obtained for such diverse organisms as *Homo sapiens* (humans), *Caenorhabditis elegans* (soil nematode), *Arabidopsis thaliana* (thale cress, a mustard) and *Oryza sativa* (rice).

As a result of extensive studies, common amino acid sequences have been deduced for homologous binding sites of various families of glycosyltransferases. For example, sialyltransferases have sialyl motifs that appear to participate in the recognition of the donor substrate, CMP-sialic acid [Paulson *et al.*, *J. Biol. Chem.*, 264:17615-17618 (1989); Datta *et al.*, *J. Biol. Chem.*, 270:1497-1500 (1995); Katsutoshi, *Trends Glycosci. Glycotech.* 8:195-215 (1996)]. The hexapeptide RDKKND in Gal α1-3 galactosyltransferase and RDKKNE in GlcNAc β1-4 galactosyltransferase have been suggested as the binding site for UDP-Gal [(Joziasse *et al.*, *J. Biol. Chem.*, 260:4941-4951 (1985), *J. Biol. Chem.*, 264:14290-14297 (1989); Joziasse, *Glycobiology*, 2:271-277 (1992)].

A small, highly-conserved motif formed by two aspartic acid residues (DXD), which is frequently surrounded by a hydrophobic region, has been identified in a large number of different eukaryotic transferases, including α-1, 3-mannosyltransferase, β-1, 4-galactosyltransfereases, α-1, 3-galactosyltransferases, glucuronyltransferases, fucosyltransferases, glycogenins and others [Wiggins *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 95:7945-7950 (1998)]. Mutation studies indicate that this motif is necessary for enzymatic activity [Busch *et al.*, *J. Biol. Chem.* 273:19566-19572 (1998); Wang *et al.*, *J. Biol. Chem.* 277:18568-18573 (2002)]. Multiple peptide alignment showed several motifs corresponding to putative catalytic domains that are conserved throughout all members of the β 3-

galactosyltransferase family, namely, a type II transmembrane domain, a conserved DxD motif, an N-glycosylation site and five conserved cysteines [Gromova *et al., Mol. Carcinog.* 32:61-72 (2001)].

Through the use of BLAST searches and multiple alignments, the E-X_7-E motif was found to be a highly conserved among the members of four families of retaining glycosyltransferases [Cid *et al., J. Biol. Chem.* 275:33614-33621 (2000)]. The O-linked acetylglucosaminyltransferases (GlcNAc) add a single β-N-acetylglucosamine moiety to specific serine or threonine hydroxyls. BLAST analyses, consensus secondary structure predictions and fold recognition studies indicate that a conserved motif in the second Rossmann domain points to the UDP-GlcNAc donor-binding site [Wrabl *et al., J. Mol. Biol.* 314:365-374 (2001)]. The β1, 3-glycosyltransferase enzymes identified to date share several conserved regions and conserved cysteine residues, all being located in the putative catalytic domain. Site-directed mutagenesis of the murine β3GatT-I gene (Accession No. AF029790) indicate that the conserved residues W101 and W162 are involved in the binding of the UDP-galactose donor, the residue W315 in the binding of the N-acetylglucosamine- β-p-nitrophenol acceptor, and the domain including E264 appears to participate in the binding of both substrates [Malissard *et al., Eur. J. Biochem.* 269:233-239 (2002)].

Expression of Proteins of Interest in Plant Host System

The nucleic acid encoding the hybrid or modified enzymes or other heterologous proteins, such as a heterologous glycoprotein may be inserted according to certain embodiments of the present invention into an appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence, or in the case of an RNA viral vector, the necessary elements for replication and translation, as well as selectable markers. These include but are not limited to a promoter region, a signal sequence, 5' untranslated sequences, initiation codon (depending upon whether or not the structural gene comes equipped with one), and transcription and translation termination sequences. Methods for obtaining such vectors are known in the art (see WO 01/29242 for review).

Promoter sequences suitable for expression in plants are described in the art, *e.g.*, WO 91/198696. These include non-constitutive promoters or constitutive promoters , such as, the nopaline synthetase and octopine synthetase promoters, cauliflower mosaic virus (CaMV) 19S and 35S promoters and the figwort mosaic virus (FMV) 35 promoter (see U.S. Pat. Nos. 5, 352,605 and 6,051,753, both of which are hereby incorporated by reference). Promoters used may also be tissue specific promoters targeted for example to the endosperm, aleurone layer, embryo, pericarp, stem, leaves, tubers, roots, and the like.

A signal sequence allows processing and translocation of a protein where appropriate. The signal can be derived from plants or could be non-plant signal sequences. The signal peptides direct the nascent polypeptide to the endoplasmic reticulum, where the polypeptide subsequently undergoes post-translational modification. Signal peptides can routinely be identified by those of skill in the art. They typically have a tripartite structure, with positively charged amino acids at the N-terminal end,

followed by a hydrophobic region and then the cleavage site within a region of reduced hydrophobicity.

The transcription termination is routinely at the opposite end from the transcription initiation regulatory region. It may be associated with the transcriptional initiation region or from a different gene and may be selected to enhance expression. An example is the NOS terminator from *Agrobacterium* Ti plasmid and the rice alpha-amylase terminator. Polyadenylation tails may also be added. Examples include but are not limited to *Agrobacterium* octopine synthetase signal, [Gielen *et al.*, *EMBO J.* 3:835-846 (1984)] or nopaline synthase of the same species [Depicker *et al.*, *Mol. Appl. Genet.* 1:561-573 (1982)].

Enhancers may be included to increase and/or maximize transcription of the heterologous protein. These include, but are not limited to peptide export signal sequence, codon usage, introns, polyadenylation, and transcription termination sites (see WO 01/29242).

Markers include preferably prokaryote selectable markers. Such markers include resistance toward antibiotics such as ampicillin, tetracycline, kanamycin, and spectinomycin. Specific examples include but are not limited to streptomycin phosphotransferase (*spt)* gene coding for streptomycin resistance, neomycin phosphotransferase (*nptII*) gene encoding kanamycin or geneticin resistance, hygromycin phosphotransferase (*hpt*) gene encoding resistance to hygromycin.

The vectors constructed may be introduced into the plant host system using procedures known in the art (reviewed in WO 01/29242 and WO 01/31045). The vectors may be modified to intermediate plant transformation plasmids that contain a region of homology to an *Agrobacterium tumefaciens* vector, a T-DNA border region from *A. tumefaciens.* Alternatively, the vectors used in the methods of the present invention may be *Agrobacterium vectors.* Methods for introducing the vectors include but are not limited to microinjection, velocity ballistic penetration by small particles with the nucleic acid either within the matrix of small beads or particles, or on the surface and electroporation. The vector may be introduced into a plant cell, tissue or organ. In a specific embodiment, once the presence of a heterologous gene is ascertained, a plant may be regenerated using procedures known in the art. The presence of desired proteins may be screened using methods known in the art, preferably using screening assays where the biologically active site is detected in such a way as to produce a detectable signal. This signal may be produced directly or indirectly. Examples of such assays include ELISA or a radioimmunoassay.

Transient Expression

The present invention specifically contemplates both stable and transient expression of the above-described hybrid enzymes. Techniques for transforming a wide variety of higher plant species for transient expression of an expression cassette are well known [see, for example, Weising *et al.*, *Ann. Rev. Genet.* 22:421-477(1988)]. Variables of different systems include type nucleic acid transferred (DNA, RNA, plasmid, viral), type of tissue transformed, means of introducing transgene(s), and conditions of transformation. For example, a nucleic acid construct may be

introduced directly into a plant cell using techniques ranging from electroporation, PEG poration, particle bombardment, silicon fiber delivery, microinjection of plant cell protoplasts or embryogenic callus or other plant tissue, or Agrobacterium-mediated transformation [Hiei *et al., Plant J.* 6:271-282 (1994)]. Because transformation efficiencies are variable, internal standards (eg, 35S-Luc) are often used to standardize transformation efficiencies.

Expression constructs for transient assays include plasmids and viral vectors. A variety of plant viruses that can be employed as vectors are known in the art and include cauliflower mosaic virus (CaMV), geminivirus, brome mosaic virus, and tobacco mosaic virus.

Plant tissues suitable for transient expression include cultured cells, either intact or as protoplasts (in which the cell wall is removed), cultured tissue, cultured plants, and plant tissue such as leaves.

Some transient expression methods utilize gene transfer into plant cell protoplasts mediated by electroporation or polyethylene glycol (PEG). These methods require the preparation and culture of plant protoplasts, and involve creating pores in the protoplast through which nucleic acid is transferred into the interior of the protoplast.

Exemplary electroporation techniques are described in Fromm *et al., Proc. Natl. Acad. Sci.* 82: 5824 (1985). The introduction of DNA constructs using polyethylene glycol precipitation is described in Paszkowski *et al., EMBO J.* 3: 2717-2722 (1984). PEG-mediated transformation of tobacco protoplasts, which includes the steps of isolation, purification, and transformation of the protoplasts, are described in Lyck *et al.,* (1997) *Planta* 202: 117-125 and Scharf *et al.,* (1998) *Mol Cell Biol* 18: 2240-2251, and Kirschner *et al.,* (2000) *The Plant J* 24(3): 397-411. These methods have been used, for example, to identify cis-acting elements in promoters activated by external stimuli, Abel and Theologis (1994) *Plant J* 5: 421-427; Hattori *et al.,* (1992) *Genes Dev* 6: 609-618; Sablowski *et al.,* (1994) *EMBO J* 13: 128-137; and Solano *et al.,* (1995) *EMBO J* 14: 1773-1784), as well as for other gene expression studies (U. S. Patent 6,376,747, hereby incorporated by reference).

Ballistic transformation techniques are described in Klein *et al.,* (1987) *Nature* 327: 70-73. Biolistic transient transformation is used with suspension cells or plant organs. For example, it has been developed for use in *Nicotiana tabacum* leaves, Godon *et al* (1993) *Biochimie* 75(7): 591-595. It has also been used in investigating plant promoters, (Baum *et al.,* (1997) *Plant J* 12: 463-469; Stromvik *et al.,* (1999) *Plant Mol Biol* 41(2): 217-31, Tuerck and Fromm (1994) *Plant Cell* 6: 1655-1663; and U. S. Patent 5,847,102, hereby incorporated by reference), and to characterize transcription factors (Goff *et al.,* (1990) *EMBO J* 9: 2517-2522; Gubler *et al.,* (1999) *Plant J* 17: 1-9; and Sainz *et al.,* (1997) *Plant Cell* 9: 611-625).

Other methods allow visualization of transient expression of genes *in situ*, such as with onion epidermal peels, in which GFP expression in various cellular compartments was observed (Scott *et al.,* (1999) *Biotechniques* 26(6): 1128-1132

Nucleic acids can also be introduced into plants by direct injection. Transient gene expression can be obtained by injection of the DNA into reproductive organs of a plant (see, for example, Pena *et al.*, (1987) Nature, 325.:274), such as by direct DNA transfer into pollen (see, for example, Zhou *et al.*, (1983) *Methods in Enzymology*, 101:433; D. Hess (1987) *Intern Rev. Cytol.*, 107:367; Luo *et al.*, (1988) *Plant Mol. Biol. Reporter*,.6:165. DNA can also be injected directly into the cells of immature embryos (see, for example, Neuhaus *et al.*, (1987) *Theor. Appl. Genet*: 75:30; and Benbrook *et al.*, (1986) in *Proceedings Bio Expo* 1986, Butterworth, Stoneham, Mass., pp. 27-54).

Agrobacterium-mediated transformation is applicable to both dicots and monocots. Optimized methods and vectors for Agrobacterium-mediated transformation of plants in the family Graminae, such as rice and maize have been described (see, for example, Heath *et al.*, (1997) *Mol. Plant-Microbe Interact.* 10:221-227; Hiei *et al.*, (1994) *Plant J.* 6:271-282 and Ishida *et al.*, (1996) *Nat. Biotech.* 14:745-750). The efficiency of maize transformation is affected by a variety of factors including the types and stages of tissue infected, the concentration of Agrobacterium, the tissue culture media, the Ti vectors and the maize genotype.

Another useful basic transformation protocol involves a combination of wounding by particle bombardment, followed by use of Agrobacterium for DNA delivery (see, for example, Bidney *et al.*, (1992) *Plant Mol. Biol.* 18:301-313). Both intact meristem transformation and a split meristem transformation methods are also known (U. S. Patent 6,300,545, hereby incorporated by reference).

Additional methods utilizing Agrobacteria include agroinfection and agroinfiltration. By inserting a viral genome into the T-DNA, Agrobacterium can be used to mediate the viral infection of plants (see, for example, U. S. Patent 6,300,545, hereby incorporated by reference). Following transfer of the T-DNA to the plant cell, excision of the viral genome from the T-DNA (mobilization) is required for successful viral infection. This Agrobacterium-mediated method for introducing a virus into a plant host is known as agroinfection (see, for example, Grimsley, "Agroinfection" pp. 325-342, in *Methods in Molecular Biology*, vol 44: Agrobacterium Protocols, ed. Gartland and Davey, Humana Press, Inc., Totowa, N.J.; and Grimsley (1990) *Physiol. Plant.* 79:147-153).

The development of plant virus gene vectors for expression of foreign genes in plants provides a means to provide high levels of gene expression within a short time. Suitable viral replicons include double-stranded DNA from a virus having a double stranded DNA genome or replication intermediate. The excised viral DNA is capable of acting as a replicon or replication intermediate, either independently, or with factors supplied in trans. The viral DNA may or may not encode infectious viral particles and furthermore may contain insertions, deletions, substitutions, rearrangements or other modifications. The viral DNA may contain heterologous DNA, which is any non-viral DNA or DNA from a different virus. For example, the heterologous DNA may comprise an expression cassette for a protein or RNA of interest.

Super binary vectors carrying the vir genes of Agrobacterium strains A281 and A348 are useful for high efficiency transformation of monocots. However, even without the use of high

efficiency vectors, it has been demonstrated that T-DNA is transferred to maize at an efficiency that results in systemic infection by viruses introduced by agroinfection, although tumors are not formed (Grimsley *et al.*, (1989) *Mol. Gen. Genet.* 217:309-316). This is because integration of the T-DNA containing the viral genome is not required for viral multiplication, since the excised viral genome acts as an independent replicon.

Another Agrobacteria-mediated transient expression assay is based on Agrobacterium-mediated transformation of tobacco leaves in planta (Yang *et al.*, (2000) *The Plant J* 22(6): 543-551). The method utilizes infiltration of agrobacteria carrying plasmid constructs into tobacco leaves, and is referred to as agroinfiltration; it has been utilized used to analyze in vivo expression of promoters and transcription factors in as little as 2-3 days. It also allows examination of effects of external stimuli such as pathogen infections and environmental stresses on promoter activity *in situ*.

Example 1

An *Arabidopsis thaliana* cDNA encoding β1,2-xylosyltransferase was isolated from a cDNA library by a previously described PCR based sibling selection procedure [Bakker *et al.*, *BBRC* 261:829 (1999)]. Xylosyltransferase activity was confirmed by immunostaining of transfected CHO cells with a xylose specific antibody purified from rabbit-anti-horseradish-peroxidase antiserum. A DNA fragment covering the N-terminal part of the xylosyltransferase was amplified using primers:

XylTpvuF:ATACTCGAGTTAACAATGAGTAAACGGAATC (SEQ ID NO:45)

and XylTpvuR:TTCTCGATCGCCGATTGGTTATTC (SEQ ID NO:46)

XhoI and HpaI restriction sites were introduced in front of the start codon and a PvuI was introduced at the reverse end. A C-terminal fragment from Human β1,4galactosyltransferase (acc.no. x55415, Aoki 1992) was amplified using primers GalTpvuF:GCCGCCGCGATCGGGCAGTCCTCC (SEQ ID NO:47) and GalTrev:AACGGATCCACGCTAGCTCGGTGTCCCGAT (SEQ ID NO:48) thus introducing PvuI and BamHI sites. The XhoI/PvuI and PvuI/BamHI digested PCR fragments were ligated in XhoI/BamHI digested pBluescriptSK+ and sequenced. The resulting open reading frame encodes a fusion protein containing the first 54 amino acids of *A. thaliana* β1,2-xylosyltransferase fused with amino acid 69 to 398 of human β1,4galactosyltransferase and is designated as TmXyl-GalT. The fragment was cloned into a plant expression vector between the CaMV35S promoter and Nos terminator, using HpaI/BamHI. The clone was introduced into *Nicotiana tabacum* (samsun NN) as described for native human β1,4galactosyltransferase [Bakker *et al.*, *Proc. Nat. Acad. Sci. USA* 98:2899 (2001)].

Protein extract of transgenic plants and Western Blots were made as described [Bakker *et al.*, *Proc. Nat. Acad. Sci. USA* 98:2899 (2001)]. Based on reaction with the lectin RCA, a transgenic plant expressing TmXylGalT was selected for further glycan analysis by MALDI-TOF [Elbers *et al.*, *Plant Physiology* 126:1314 (2001] and compared with glycans isolated from plants expressing native β1,4galactosyltransferase and with glycans from wild-type plants. Relative peak areas of the

MALDI-TOF spectrum are given in Table 1. That is to say, Table 1 is a comparison of the results of mass spec (MALDI-TOF) analysis of N-glycans of endogenous glycoproteins of control tobacco ("Tobacco"), transgenic tobacco expressing human beta-1,4-galactosyltransferase ("GalT") and transgenic tobacco plants expressing the beta-1,4-galactosyltransferase gene of which the CTS region has been replaced with that of beta-1,2-xylosyltransferase ("TmXyl-GalT").

TABLE 1					
m/z		Type	Tobacco	GalT	TmXyl-GalT
933		M3		3	7
1065		XM3	10	16	3
1079		FM3			4
1095		M4			9
1211		FXM3	41	27	
1257		M5	4	5	23
1268		GNXM3		4	
1298		GalGNM3			6
1298		GNM4			
1414		GNFXM3	27	13	5
1419		M6	7	8	10
1460		GalGNM4			11
1460		GNM5			
1485		GN2FM3		4	
1576		GalGNFXM3		5	
1576		GNFXM4			
1581		M7	3		4
1606		GNFM5			3
1606		GalGNFM4			
1617		GN2FXM3	8	9	
1622		GalGNM5			9
1622		GNM6			
1743		M8		2	3
1768		GalGNFM5			3
1768		GNFM6			
1779		GalGN2FXM3		2	
1905		M9			1
1941		Gal2GN2FXM3		2	
		TOTAL	100	100	101

These data show that:

1. In TmXylGalT plants, xylosylation and fucosylation of the glycans is dramatically reduced: 82% of the glycans do not carry xylose nor fucose as compared to 14% in wild-type plants.
2. Galactosylation has increased from 9% in GalT plants to 32% in TmXylGalT plants.

Example 2

A transgenic plant expressing said TmXyl-GalT gene (TmXyl-GalT-12 plant) was selected (above) based on lectin blotting using biotin-labelled RCA (Vector Laboratories, Burlingame, California). Comparison of protein extracts of MGR48 transgenic (control) plant, a selected transgenic plant expressing the unmodified human β1,4-galactosyltransferase gene and TmXyl-GalT-12 plant for the presence of xylose and fucose using anti-HRP (horseradish peroxidase) polyclonal antibody (known for high anti-xylose and anti-fucose reactivity) clearly showed reduced xylose and fucose (Figure 34: "Anti-HRP"). Western blotting using an anti-xylose fraction of the anti-HRP and an anti-fucose fraction (each of which can be prepared by affinity chromatography over the appropriate ligand) showed that especially xylose was reduced compared to control plants (Figure 34: anti-Fuc" and "anti-Xyl").

Example 3

The TmXyl-GalT-12 plant was crossed with a transgenic plant expressing the monoclonal antibody MGR48 from a single T-DNA integration event (MGR48-31) and which was first made homozygous by selecting offspring plants not segregating for the kanamycin resistance marker and antibody production (MGR48-31-4). Pollen of MGR48-31-4 was used for pollination of emasculated TmXyl-GalT-12 plants. Vice versa, pollen of TmXyl-GalT-12 plant was used for fertilization on emasculated MGR48-31-4 plants. A number of F1 plants were analyzed for the presence of MGR48 by western blotting and for galactosylation of endogenous glycoproteins by lectin blotting using RCA (Figure 35). One plant expressing MGR48 and showing galactosylation of endogenous glycoproteins was selected for further analysis. This plant was identified as XGM8.

Seeds from TmXyl-GalT-12 (♀) x MGR48-31-4 (♂) were sown and F1 offspring plants (XGM) were analysed for antibody production by Western blotting and for galactosylation by lectin blotting using biotinylated RCA120 (Vector Labs., Burlingame, California) using standard techniques as described before. All plants as expected expressed the monoclonal antibody MGR48 and the majority also had galactosylated glycans as depicted from lectin blotting using RCA120. A single plant expressing both antibody MGR48 and having galactosylated N-glycans was chosen for further analysis (XGM8) (TmXyl-GalT-12 X MGR48-31-4 offpring plant 8). The monoclonal recombinant MGR48 antibody was purified from this plant as described before and submitted to N-glycan analysis by MALDI-TOF.

Briefly, XGM8 plant was grown in greenhouse for antibody production under optimal conditions [Elbers *et al.*, *Plant Physiology* 126:1314 (2001)]. Protein extract of leaves of transgenic XGM8 plant was made and monoclonal antibody was purified using protein G chromatography as described [Bakker et al, *Proc. Nat. Acad. Sci. USA* 98:2899 (2001)]. MALDI-TOF of N-glycans of purified monoclonal antibody was as described (Elbers *et al.*, 2001, supra). The presence of galactose on glycans was established by enzyme sequencing using bovine testis β-galactosidase as described (Bakker *et al.*, 2001, supra; Table 2). Table 2 (below) is a comparison of the results of

mass spec (MALDI-TOF) analysis of N-glycans of endogenous glycoproteins ("Xyl-GalT Endo") of a F1 hybrid of TmXyl-GalT-12plant and plant producing rec-mAb (MGR48) and of N-glycans of rec-mAB purified by protein G chromatography from said F1 hybrid.

TABLE 2			Xyl-GalT	Xyl-GalT
m/z		Type	Endo	IgG
933		M3	6	4
1065		XM3	2	2
1079		FM3	2	3
1095		M4	5	5
1136		GNM3	1	2
1211		FXM3	6	3
1241		FM4	3	2
1257		M5	17	12
1268		GNXM3	1	2
1282		GNFM3	2	3
1298		GalGNM3	3	4
1403		FM5	4	3
1414		GNFXM3	2	4
1419		M6	5	4
1430		GNXM4	2	2
1430		GalGNXM3		
1444		GNFM4	1	3
1444		GalGNFM3		
1460		GalGNM4	8	10
1460		GNM5		
1471		GN2XM3	1	
1485		GN2FM3	1	1
1501		GalGN2M3	1	1
1576		GalGNFXM3	2	3
1576		GNFXM4		
1581		M7	2	2
1593		GalGNXM4	1	2
1593		GNXM5		
1606		GNFM5	3	4
1606		GalGNFM4		
1617		GN2FXM3	2	1
1622		GalGNM5	6	6
1622		GNM6		
1647		GalGN2FM3	1	1
1663		Gal2GN2M3	1	1
1738		GNFXM5	1	2
1738		GalGNFXM4		
1743		M8	1	2
1754		GalGNXM5	1	2
1768		GalGNFM5	2	3
1768		GNFM6		

1784		GNM7	1	1
1784		GalGNM6		
1809		Gal2GN2FM3	2	1
1900		GNFXM6	1	
1900		GalGNFXM5		
1905		M9	1	1
		TOTAL	101	102

These data show that:

1. In the F1 hybrid, xylosylation and fucosylation of the glycans is dramatically reduced: 43% of the glycans of endogenous glycoproteins lack xylose and fucose as compared to only 14% in wild-type tobacco plants.
2. The glycans of purified mAb of this F1 hybrid have reduced xylose and fucose, 47% compared to 14% for wildtype tobacco. See also Figure 36, panels B-D.
3. Galactosylation of endogenous glycoproteins of F1 hybrid has increased from 9% in GalT plants to 37% in F1 TmXyl-GalT X MGR48 plant. See also Figure 35.
4. Purified rec-mAb from said F1 (see Figure 36, panel A) shows increased galactosylation; that is to say, 46% has galactose. See also Figure 36, panel E.

It should however be noted that the observed quantities (MALDI-TOF) do not necessarily reflect the molar rations of said glycoforms in vivo. Quantification based on MALDI-TOF can be under- or overestimated depending on the specific glycoform under study. Also, since there is no molecular weight difference between Gal and Man, some peaks can not be annotated unambiguously unless there are clear differences in relative height of specific molecules before and after galactosidase treatment.

Example 4

A more direct comparison of xylose, fucose and galactose content was done by examining the MGR48 IgG antibodies from hybridoma, transgenic tobacco and TmXyl-GalT transgenic tobacco. As mentioned above, the TmXyl-GalT-12 plant was crossed with tobacco plant expressing MGR48 IgG (MGR48 tobacco) resulting in an F1 hybrid harbouring MGR48 TmXyl-GalT. An F1 plant was chosen for extraction and purification of MGR48 IgG. Antibodies from said plants (tobacco and TmXyl-GalT) were isolated and purified using protein G chromatography (Elbers *et al.*, 2001. *Plant Physiology* 126: 1314-1322). 300 nanograms amounts of each, hybridoma MGR48 and plant-derived recMGR48, were loaded on precast 12% SDS-PAGE gels (BioRad) and run. The contents of each lane were as follows: Lane 1, MGR48 from hybridoma; Lane 2, purified recMGR48 from normal transgenic tobacco plant; and Lane 3, purified recMGR48 from TmXyl-GalT transgenic plant. Following SDS-PAGE proteins were transferred to nitrocellulose using CAPS buffer. Blots were incubated with A, anti-mouse IgG; B, polyclonal rabbit anti-HRP (anti-xylose/(alpha 1,3-fucose); C, anti-xylose; D, anti-(alpha 1,3-) fucose antibodies; and E, biotinylated RCA. Detection

was with LumiLight on Lumi Imager following incubation with HRP-labelled sheep anti-mouse (panel A) or goat-anti-rabbit (panels B-D) antibodies and HRP-labeled streptavidin (E).

Panel A shows that approximately similar amounts of the MGR48 IgG was loaded for all lanes (1-3). L refers to Light chain and H, heavy chain of MGR48 IgG.

Panel B shows that the heavy chain of MGR48 antibody in lane 2 (tobacco) strongly reacts with anti-HRP as expected, whereas the heavy chain of hybridoma derived MGR48 (lane 1) does not (as expected). Hybridoma derived antibodies do not carry xylose and alpha 1, 3-fuctose residues. Remarkably, MGR48 antibodies from TmXyl-GalT tobacco plant also do not react, suggesting that the heavy chain of antibody from this plant have significantly reduced (perhaps by 90% or more) the amounts of xylose and fucose residues on the N-glycans. This is confirmed by experiments depicted in panels C (anti-xylose) and D (anti-fucose). Panel E shows that the heavy chain of MGR48 antibody of hybridoma (lane 1) has a galactosylated N-glycan, whereas tobacco-derived MGR48 (lane 2) has not, both as expected. Heavy chain of MGR48 from the TmXyl-GalT plant (lane 3) also has galactosylated N-glycan due to the presence of the construct expressing the hybrid enzyme.

These data are in agreement with the data obtained from similar experiments using total protein extracts from similar plants (tobacco and TmXyl-GalT-12 plant) as shown previously and confirm that the novel trait introduced in tobacco from expression of TmXyl-GalT gene can be stably transmitted to offspring and a recombinant monoclonal antibody.

Example 5

Further characterization of the above-described F1 hybrid was performed by treatement with beta-galactosidase. Table 3 is a comparison of the results of mass spec (MALDI-TOF) analysis of N-glycans of rec-mAbs purified by protein G chromatography from an F1 hybrid of TmXyl-GalT and MGR48 plant before and after treatment of the glycans with beta-galactosidase.

TABLE 3			Xyl-GalT	Xyl-GalT
m/z		Type	IgG-	IgG+beta-galactosidase
933		M3	4	4
1065		XM3	2	2
1079		FM3	3	3
1095		M4	5	4
1136		GNM3	2	3
1211		FXM3	3	4
1241		FM4	2	2
1257		M5	12	13
1268		GNXM3	2	3
1282		GNFM3	3	3
1298		GalGNM3	4	4
1403		FM5	3	2
1414		GNFXM3	4	5
1419		M6	4	3

1430		GNXM4	2	2
1430		GalGNXM3		
1444		GNFM4	3	3
1444		GalGNFM3		
1460		GalGNM4	10	14
1460		GNM5		
1471		GN2XM3		1
1485		GN2FM3	1	1
1501		GalGN2M3	1	
1576		GalGNFXM3	3	3
1576		GNFXM4		
1581		M7	2	2
1593		GalGNXM4	2	2
1593		GNXM5		
1606		GNFM5	4	6
1606		GalGNFM4		
1617		GN2FXM3	1	1
1622		GalGNM5	6	1
1622		GNM6		
1647		GalGN2FM3	1	
1663		Gal2GN2M3	1	
1738		GNFXM5	2	2
1738		GalGNFXM4		
1743		M8	2	2
1754		GalGNXM5	2	1
1768		GalGNFM5	3	1
1768		GNFM6		
1784		GNM7	1	1
1784		GalGNM6		
1809		Gal2GN2FM3	1	
1900		GNFXM6		1
1900		GalGNFXM5		
1905		M9	1	1
		TOTAL	102	100

These data show that:

1. Rec-mAbs from F1 hybrid contain galactose which can be deduced from the observed reduction of specific (galactose-containing) glycoforms after beta-galactosidase treatment and increase of glycoforms lacking galactose. Note the observed reduction of m/z 1622 from 6 to 1% and simultaneous increase of m/z 1460 from 10 to 14% which is the result of the removal of galactose from GalGNM5 to give rise to GNM5. The same is true for m/z 1768 (3 to 1% decrease) and corresponding m/z 1606 peak (4 to 6% increase). See also Figure 36, panel E.
2. Similarly a number of peaks that can be attributed to galactose containing glycans vanish upon treatment with galactosidase, especially m/z 1501, 1647 and 1663 confirming the presence of galactose.

Example 6

In another embodiment, the aminoterminal CTS region of an insect Mannosidase III gene (accession number: AF005034; mistakenly annotated as a Mannosidase II gene!) is replaced by a mouse signal peptide coding sequence for import into the endoplasmic reticulum (see Figure 37). The signal peptide sequence encodes a fully active signal peptide normally present at the aminoterminus of IgG sequences and has been used successfully in plants and other organisms before. Furthermore a synthetic sequence coding for a so-called endoplasmic reticulum retention sequence (KDEL) is added to the carboxyterminus of the gene part encoding the catalytic fragment for ER retention. The hybrid Mannosidase III protein encoded by this gene sequence will hence accumulate preferentially in the endoplasmic reticulum.

Example 7

In another embodiment, the aminoterminal CTS region of the human beta-1,4-galactosyltransferase (GalT) gene (accession A52551) is replaced by a mouse signal peptide coding sequence for import into the endoplasmic reticulum (see Figure 39). The signal peptide sequence encodes a fully active signal peptide normally present at the aminoterminus of IgG sequences and has been used successfully in plants and other organisms before. Furthermore a synthetic sequence coding for a so-called endoplasmic reticulum retention sequence (KDEL) is added to the carboxyterminus of the gene part encoding the catalytic fragment for ER retention. The hybrid beta-1,4-galactosyl-transferase protein encoded by this gene sequence will hence accumulate preferentially in the endoplasmic reticulum.

Example 8

In another embodiment, the aminoterminal CTS region of *Arabidopsis thaliana* GnTI (acc. AJ243198) is replaced by a mouse signal peptide coding sequence for import into the endoplasmic reticulum (see Figure 41). The signal peptide sequence encodes a fully active signal peptide normally present at the aminoterminus of IgG sequences and has been used successfully in plants and other organisms before. Furthermore a synthetic sequence coding for a so-called endoplasmic reticulum retention sequence (KDEL) is added to the carboxyterminus of the gene part encoding the catalytic fragment for ER retention. The hybrid GnTI protein encoded by this gene sequence will hence accumulate preferentially in the endoplasmic reticulum.

Example 9

In another embodiment, the aminoterminal CTS region of an *Arabidopsis thaliana* GnTII (acc. AJ249274) is replaced by a mouse signal peptide coding sequence for import into the endoplasmic reticulum (see Figure 43). The signal peptide sequence encodes a fully active signal peptide normally present at the aminoterminus of IgG sequences and has been used successfully in

plants and other organisms before. Furthermore a synthetic sequence coding for a so-called endoplasmic reticulum retention sequence (KDEL) is added to the carboxyterminus of the gene part encoding the catalytic fragment for ER retention. The hybrid GnTII protein encoded by this gene sequence will hence accumulate preferentially in the endoplasmic reticulum.

Example 10

In another embodiment, the aminoterminal CTS region of the human gene for beta-1,4-galactosyltransferase (GalT) gene is replaced by the CTS region of the human gene for GnTI (TmhuGnTI-GalT) (see Figure 45).

It is understood that the present invention is not limited to any particular mechanism. Nor is it necessary to understand the mechanism in order to successfully use the various embodiments of the invention. Nonetheless, it is believed that there is a sequential distribution of Golgi enzymes (Figure 47) and that the swapping in of transmembrane domains of plant glycosyltransferases causes relocalization (Figure 48).

It is understood that the present invention is not limited to the particular methodology, protocols, cell lines, vectors, and reagents described herein, as these may vary. It is also to be understood that the terminology used herein is used for the purpose of describing particular embodiments only, and is not intend to limit the scope of the present invention. It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs.

The invention described and claimed herein is not to be limited in scope by the specific embodiments herein disclosed, since these embodiments are intended as illustrations of several aspects of the invention. Any equivalent embodiments are intended to be within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

Various references are cited herein, the disclosures of which are incorporated by reference in their entireties.

WHAT IS CLAIMED IS:

1. Nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising a transmembrane region of a plant glycosyltransferase and a catalytic region of a mammalian glycosyltransferase.

2. The nucleic acid of Claim 1, wherein said plant glycosyltransferase is a xylosyltransferase.

3. The nucleic acid of Claim 1, wherein said plant glycosyltransferase is a N-acetylglucosaminyltransferase.

4. The nucleic acid of Claim 1, wherein said plant glycosyltransferase is a fucosyltransferase.

5. The nucleic acid of Claim 1, wherein said mammalian glycosyltransferase is a human galactosyltransferase.

6. The nucleic acid of Claim 5, wherein said human galactosyltransferase is encoded by at least a portion of the nucleic acid sequence of SEQ ID NO:1.

7. An expression vector, comprising the nucleic acid of Claim 1.

8. A host cell transfected with the vector of Claim 7.

9. The host cell of Claim 8, wherein said host cell is a plant cell.

10. A cell suspension comprising the host cell of Claim 9.

11. The hybrid enzyme expressed by the plant cell of Claim 9.

12. The plant comprising the host cell of Claim 9.

13. Nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising a transmembrane region of a first glycosyltransferase and a catalytic region of a second glycosyltransferase.

14. The nucleic acid of Claim 13, wherein said first glycosyltransferase comprises a plant glycosyltransferase

15. The nucleic acid of Claim 14, wherein said plant glycosyltransferase is a xylosyltransferase.

16. The nucleic acid of Claim 14, wherein said plant glycosyltransferase is a fucosyltransferase.

17. The nucleic acid of Claim 13, wherein said second glycosyltransferase comprises a mammalian glycosyltransferase.

18. The nucleic acid of Claim 17, wherein said mammalian glycosyltransferase is a human galactosyltransferase.

19. The nucleic acid of Claim 13, wherein said first glycosyltransferase comprises a first mammalian glycosyltransferase and said second glycosyltransferase comprises a second mammalian glycosyltransferase.

20. The nucleic acid of Claim 19, wherein said first mammalian glycosyltransferase is a non-human glycosyltransferase.

21. The nucleic acid of Claim 19, wherein said second mammalian glycosyltransferase is a human glycosyltransferase.

22. A method, comprising:

a. providing: i) a plant cell, and ii) an expression vector comprising nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising a transmembrane region of a plant glycosyltransferase and a catalytic region of a mammalian glycosyltransferase; and

b. introducing said expression vector into said plant cell under conditions such that said hybrid enzyme is expressed.

23. The method of Claim 22, wherein said plant glycosyltransferase is a xylosyltransferase.

24. The method of Claim 23, wherein said plant glycosyltransferase is a N-acetylglucosaminyltransferase.

25. The method of Claim 23, wherein said plant glycosyltransferase is a fucosyltransferase.

26. The method of Claim 22, wherein said mammalian glycosyltransferase is a human galactosyltransferase.

27. The nucleic acid of Claim 26, wherein said human galactosyltransferase is encoded by at least a portion of the nucleic acid sequence of SEQ ID NO:1.

28. A method, comprising:

a. providing: i) a plant cell, ii) a first expression vector comprising nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising a transmembrane region of a plant glycosyltransferase and a catalytic region of a mammalian glycosyltransferase, and iii) a second expression vector comprising nucleic acid encoding a heterologous glycoprotein; and

b. introducing said first and second expression vectors into said plant cell under conditions such that said hybrid enzyme and said heterologous protein are expressed.

29. The method of Claim 28, wherein said heterologous protein is an antibody or antibody fragment.

30. A method, comprising:

a) providing: i) a first plant comprising a first expression vector, said first vector comprising nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising at least a portion of a transmembrane region of a plant glycosyltransferase and at least a portion of a catalytic region of a mammalian glycosyltransferase, and ii) a second plant comprising a second expression vector, said second vector comprising nucleic acid encoding a heterologous protein; and

b) crossing said first plant and said second plant to produce progeny expressing said hybrid enzyme and said heterologous protein.

31. A plant, comprising first and second expression vectors, said first vector comprising nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising at least a portion of a transmembrane region of a plant glycosyltransferase and at least a portion of a catalytic region of a mammalian glycosyltransferase, said second vector comprising nucleic acid encoding a heterologous protein.

32. The plant of Claim 31, wherein said heterologous protein displays reduced amounts of fucose as compared to when the heterologous protein is expressed in a plant in the absence of said hybrid enzyme

33. The plant of Claim 31, wherein the heterologous protein displays reduced amounts of xylose as compared to when the heterologous protein is expressed in a plant in the absence of said hybrid enzyme.

34. The plant of Claim 31, wherein the heterologous protein displays both reduced fucose and xylose, as compared to when the heterologous protein is expressed in a plant in the absence of said hybrid enzyme.

35. The plant of Claim 31, wherein the heterologous protein displays complex type bi-antannery glycans and contains galactose residues on at least one of the arms.

36. Nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising a modified mammalian glycosyltransferase, wherein a transmembrane portion has been deleted and endoplasmic reticulum retention signal have been inserted.

37. Nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising a CTS region or portion thereof of a plant glycosyltransferase and a catalytic region of a mammalian glycosyltransferase, wherein said CTS region is from a N-acetylglucosaminyltransferase I (GnTI) and said catalytic region is from a mannosidase II (ManII).

38. Nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising a CTS region or portion thereof of a plant glycosyltransferase and a catalytic region of a mammalian glycosyltransferase, wherein said CTS region or portion thereof is from a N-acetylglucosaminyltransferase I (GnTI) and said catalytic region is from a N-acetylglucosaminyltransferase II (GnTII).

39. A plant host system, comprising (a) a nucleic acid sequence encoding a Mannosidase III glycosyltransferase; (b) a nucleic acid sequence encoding a hybrid enzyme, said hybrid enzyme comprising a CTS region or portion thereof of a plant glycosyltransferase and a catalytic domain of a mammalian glycosyltransferase

40. A method, comprising (a) introducing into said plant host system a vector comprising (i) a nucleic acid sequence encoding a hybrid enzyme comprising a catalytic region of a galactosyltransferase not normally found in a plant and a transmembrane region of a protein, (ii) a nucleic acid sequence encoding a hybrid enzyme comprising a transmembrane region of a N-acetylglucosaminyltransferase I (GnTI) and a catalytic region of a mannosidase II (ManII), (iii) a nucleic acid sequence encoding a hybrid enzyme comprising a transmembrane region of an N-acetylglucosaminyltransferase I (GnTI) and a catalytic region of a N-acetylglucosaminyltransferase II (GnTII); and (b) isolating a plant or portion thereof expressing said nucleic acid sequences.

41. A method, comprising:

a. providing: i) a host cell, and ii) an expression vector comprising nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising a transmembrane region of a first glycosyltransferase and a catalytic region of a second glycosyltransferase; and
b. introducing said expression vector into said host cell under conditions such that said hybrid enzyme is expressed.

42. The method of Claim 41, wherein said first glycosyltransferase comprises a plant glycosyltransferase.

43. The method of Claim 42, wherein said plant glycosyltransferase is a xylosyltransferase.

44. The method of Claim 42, wherein said plant glycosyltransferase is a N-acetylglucosaminyltransferase.

45. The method of Claim 42, wherein said plant glycosyltransferase is a fucosyltransferase.

46. The method of Claim 41, wherein said second glycosyltransferase comprises a mammalian glycosyltransferase.

47. The method of Claim 46, wherein said mammalian glycosyltransferase is a human galactosyltransferase.

48. A method, comprising:

a. providing: i) a host cell, ii) a first expression vector comprising nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising a transmembrane region of a first glycosyltransferase and a catalytic region of a second glycosyltransferase, and iii) a second expression vector comprising nucleic acid encoding a heterologous glycoprotein; and

b. introducing said first and second expression vectors into said host cell under conditions such that said hybrid enzyme and said heterologous protein are expressed.

49. The method of Claim 48, wherein said heterologous protein is an antibody or antibody fragment.

50. The method of Claim 48, further comprising the step of c) isolating said heterologous protein.

51. The isolated heterologous protein produced according to the method of Claim 50.

52. A host cell, comprising first and second expression vectors, said first vector comprising nucleic acid encoding a hybrid enzyme, said hybrid enzyme comprising at least a portion of a transmembrane region of a first glycosyltransferase and at least a portion of a catalytic region of a second glycosyltransferase, said second vector comprising nucleic acid encoding a heterologous protein.

53. The heterologous protein isolated from the host cell of Claim 52.

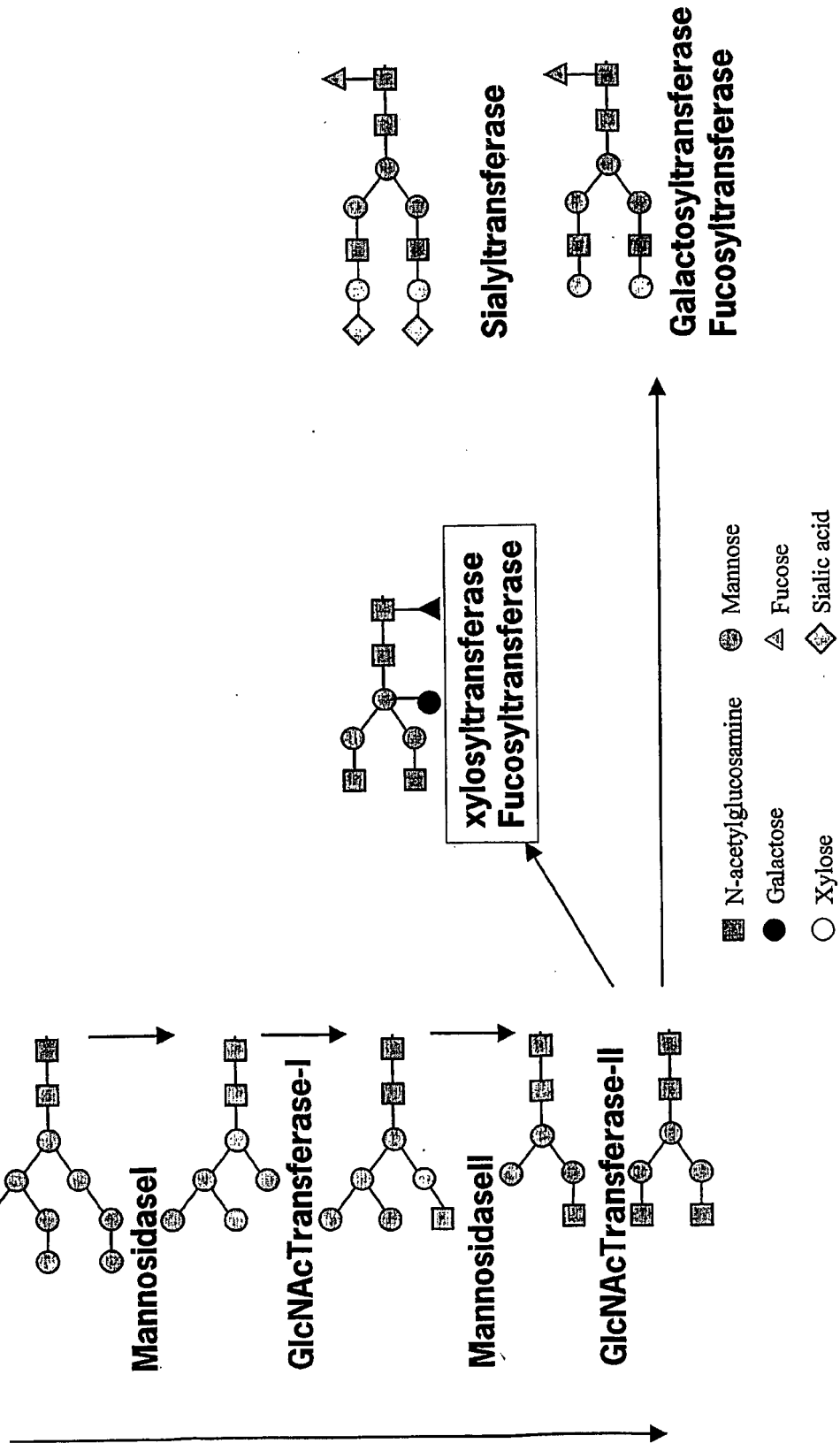
Common
Plants
Mammals
Mannosidasel
GlcNAcTransferase-I
Mannosidasell
GlcNAcTransferase-II
xylosyltransferase
Fucosyltransferase
Sialyltransferase
Galactosyltransferase
Fucosyltransferase
N-acetylglucosamine
Mannose
Galactose
Fucose
Xylose
Sialic acid

FIG. 1

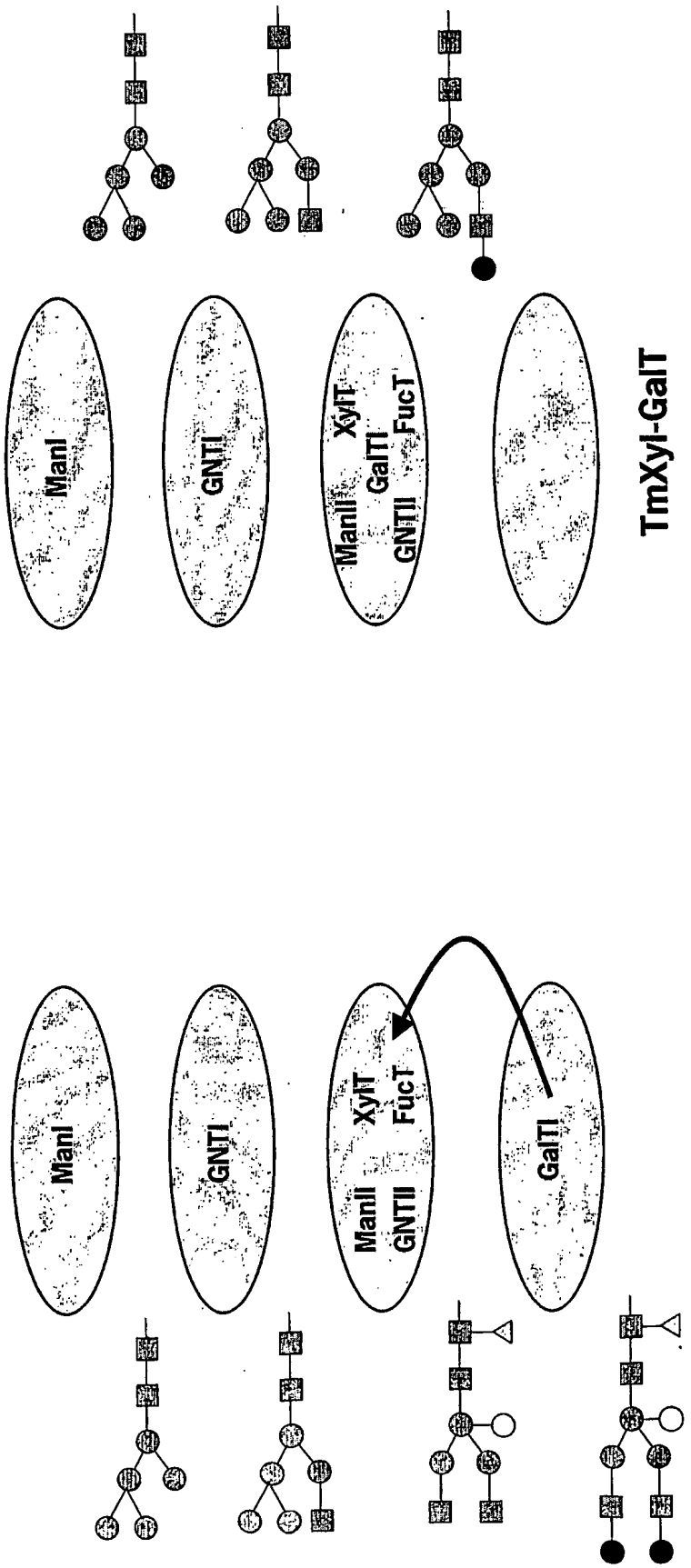
ManI
GNTI
ManII
GNTII
XylT
GalTI
FucT
TmXyl-GalT
N-acetylglucosamine
Galactose
Xylose
Mannose
Fucose

FIG. 2

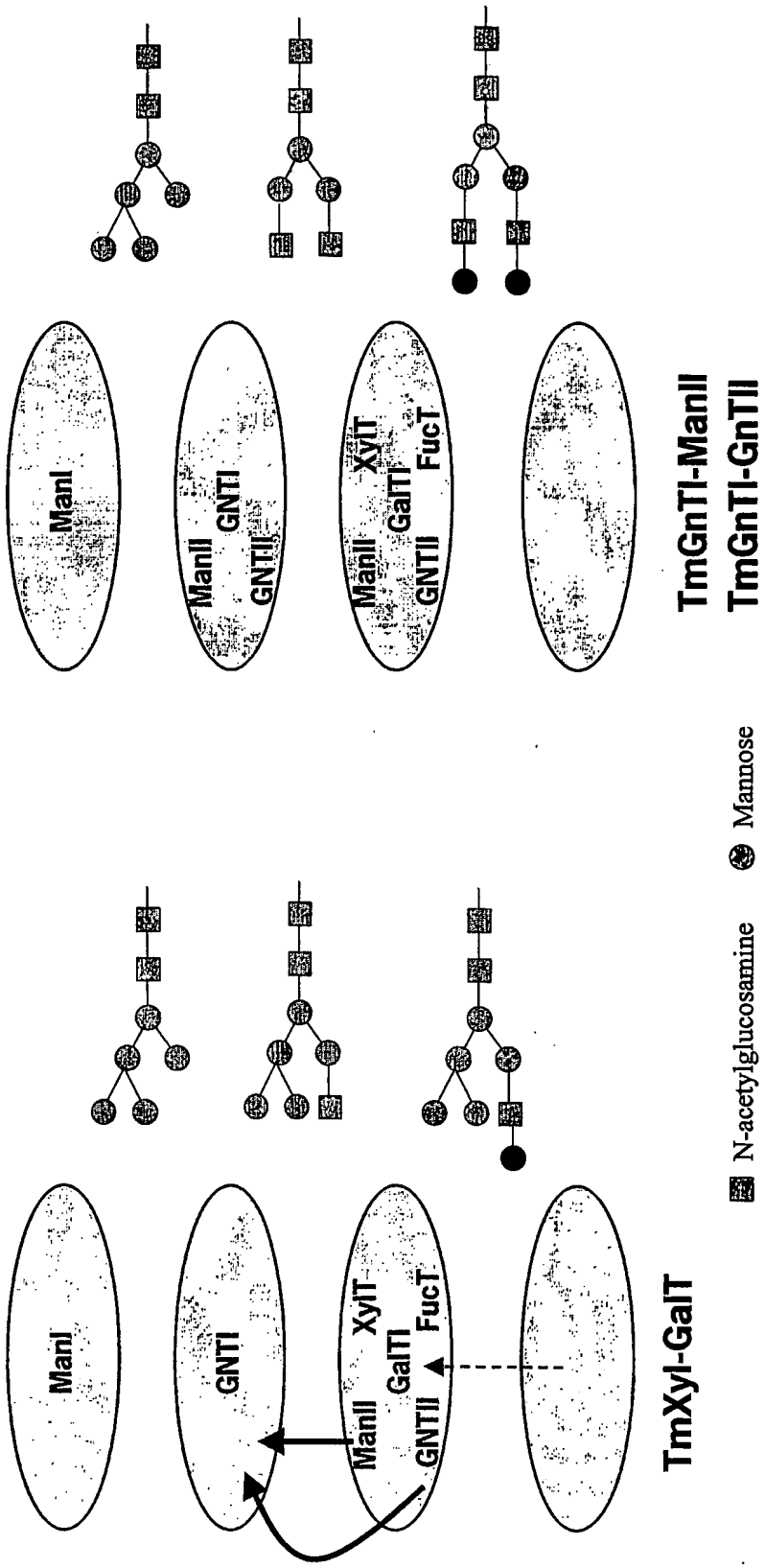
ManI
GNTI
ManII
XylT
GalTI
FucT
GNTII
TmXyl-GalT
TmGnTI-ManII
TmGnTI-GnTII
N-acetylglucosamine
Galactose
Xylose
Mannose
Fucose

FIG. 3

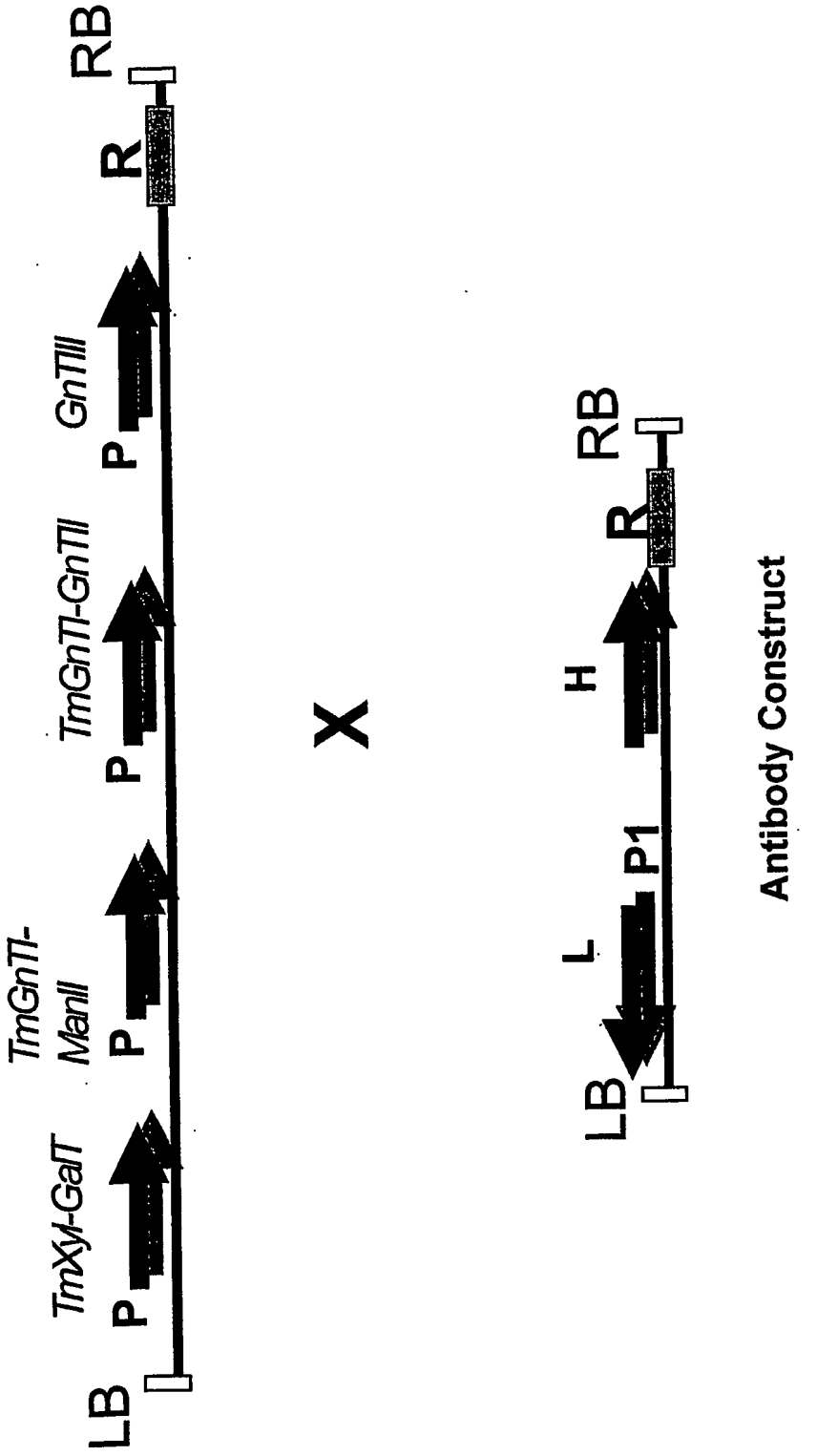
LB
P
TmXyl-GalT
TmGnTI-
ManII
P
P
TmGnTI-GnTII
P
GnTIII
R
RB
X
LB
L
P1
H
R
RB
Antibody Construct

FIG. 4

Atggcttcgggagccgctcctgagcggcagcgccgcgatgccaggcgtccctacagcgggcctgccgcctgctcgtggccgtctgcacctgcgtctgcacctggccg
cgacctgagccgcctgccccaactggtcggagtctccacaccgctgcaggggcggctcgaacagtgccgccgccatcgggcagtcctcgggggagctccggaccggagggcccggccgcccgctcctctag
gcgcctcctccagccgcgcccgggtggcgactccagcccagtcgtggattctggccctggccccgctagcaacttgacctcggtcccagtgcccacaccaccgcactgtcgctgcccgcctgcccctgaggag
tccccgctgcttgtgggcccccatgctgattgagtttaacatgcctgtggacctggaagtctcgtggcaaagcagaacccaaatgtgaagatgggcggccgctatgcccccagggactgcgtctcctccacaaggtgg
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tctgatggtttgaactcactcacctaccagggtgctggatgtacagagatacccattgtatacccaaatcacagtggacatcgggacaccgagctag

FIG. 5

atgaggcttcgggagccgctcctgagcggcagcgccgcgatgccaggcgcgtccctacag
M R L R E P L L S G S A A M P G A S L Q
cgggcctgccgcctgctcgtggccgtctgcgctctgcaccttggcgtcaccctcgtttac
R A C R L L V A V C A L H L G V T L V Y
tacctggctggccgcgacctgagccgcctgccccaactggtcggagtctccacaccgctg
Y L A G R D L S R L P Q L V G V S T P L
cagggcggctcgaacagtgccgccgccatcgggcagtcctccggggagctccggaccgga
Q G G S N S A A A I G Q S S G E L R T G
ggggcccggccgccgcctcctctaggcgcctcctcccagccgcgcccgggtggcgactcc
G A R P P P P P L G A S S Q P R P G G D S
agcccagtcgtggattctggccctggccccgctagcaacttgacctcggtcccagtgccc
S P V V D S G P G P A S N L T S V P V P
cacaccaccgcactgtcgctgcccgcctgccctgaggagtccccgctgcttgtgggcccc
H T T A L S L P A C P E E S P L L V G P
atgctgattgagtttaacatgcctgtggacctggagctcgtggcaaagcagaacccaaat
M L I E F N M P V D L E L V A K Q N P N
gtgaagatgggcggccgctatgcccccagggactgcgtctctcctcacaaggtggccatc
V K M G G R Y A P R D C V S P H K V A I
atcattccattccgcaaccggcaggagcacctcaagtactggctatattatttgcaccca
I I P F R N R Q E H L K Y W L Y Y L H P
gtcctgcagcgccagcagctggactatggcatctatgttatcaaccaggcgggagacact
V L Q R Q Q L D Y G I Y V I N Q A G D T
atattcaatcgtgctaagctcctcaatgttggctttcaagaagccttgaaggactatgac
I F N R A K L L N V G F Q E A L K D Y D
tacacctgctttgtgtttagtgacgtggacctcattccaatgaatgaccataatgcgtac
Y T C F V F S D V D L I P M N D H N A Y
aggtgtttttcacagccacggcacatttccgttgcaatggataagtttggattcagccta
R C F S Q P R H I S V A M D K F G F S L
Ccttatgttcagtattttggaggtgtctctgctctaagtaaacaacagtttctaaccatc
P Y V Q Y F G G V S A L S K Q Q F L T I
aatggatttcctaataattattggggctggggaggagaagatgatgacatttttaacaga
N G F P N N Y W G W G G E D D D I F N R
ttagtttttagaggcatgtctatatctcgcccaaatgctgtggtcgggaggtgtcgcatg
L V F R G M S I S R P N A V V G R C R M
atccgccactcaagagacaagaaaaatgaacccaatcctcagaggtttgaccgaattgca
I R H S R D K K N E P N P Q R F D R I A
cacacaaaggagacaatgctctctgatggtttgaactcactcacctaccaggtgctggat
H T K E T M L S D G L N S L T Y Q V L D
gtacagagatacccattgtatacccaaatcacagtggacatcgggacaccgagctag
V Q R Y P L Y T Q I T V D I G T P S –

FIG. 6

MRLREPLLSGAAMPGASLQRACRLLVAVCALHLGVTLVYYLAGRDLSRLPQLVGVSTPLQGGSNSAAAIGQSSGELRTGGARPPPPLG
ASSQPRPGGDSSPVVDSGPGPASNLTSVPVPHTTALSLPACPEESPLLVGPMLIEFNMPVDLELVAKQNPNVKMGGRYAPRDCVSPHKV
AIIIPFRNRQEHLKYWLYYLHPVLQRQQLDYGIYGIYVINQAGDTIFNRAKLLNVGFQEALKDYDYTCFVFSDVDLIPMNDHNAYRCFS
QPRHISVAMDKFGFSLPYVQYFGGVSALSKQQFLTINGFPNNYWGWGGEDDDIFNRLVFRGMSISRPNAVVGRCRMIRHSRDKKNEPN
PQRFDRIAHTKETMLSDGLNSLTYQVLDVQRYPLYTQITVDIGTPS

FIG. 7

ATGAGTAAACGGAATCCGAAGATTCTGAAGATTTTTCTGTATATGTTACTTCTCAACTCTCTCTTTCTCATCATCTACTTCGTTTTT
CACTCATCGTCGTTTTCACCGGAGCAGTCACAGCCTCCTCATATATACCACGTTTCAGTGAATAACCAATCGGCGAtcgggcagtcctccg
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ctag

FIG. 8

atgagtaaacggaatccgaagattctgaagatttttctgtatatgttacttctcaactct
M S K R N P K I L K I F L Y M L L L N S
ctctttctcatcatctacttcgtttttcactcatcgtcgttttcaccggagcagtcacag
L F L I I Y F V F H S S S F S P E Q S Q
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P P H I Y H V S V N N Q S A I G Q S S G
gagctccggaccggaggggcccggccgccgcctcctctaggcgcctcctcccagccgcgc
E L R T G G A R P P P P L G A S S Q P R
ccgggtggcgactccagcccagtcgtggattctggccctggccccgctagcaacttgacc
P G G D S S P V V D S G P G P A S N L T
tcggtcccagtgccccacaccaccgcactgtcgctgcccgcctgccctgaggagtccccg
S V P V P H T T A L S L P A C P E E S P
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L L V G P M L I E F N M P V D L E L V A
Aagcagaacccaaatgtgaagatgggcggccgctatgcccccagggactgcgtctctcct
K Q N P N V K M G G R Y A P R D C V S P
cacaaggtggccatcatcattccattccgcaaccggcaggagcacctcaagtactggcta
H K V A I I I P F R N R Q E H L K Y W L
tattatttgcacccagtcctgcagcgccagcagctggactatggcatctatgttatcaac
Y Y L H P V L Q R Q Q L D Y G I Y V I N
caggcgggagacactatattcaatcgtgctaagctcctcaatgttggctttcaagaagcc
Q A G D T I F N R A K L L N V G F Q E A
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L K D Y D Y T C F V F S D V D L I P M N
gaccataatgcgtacaggtgtttttcacagccacggcacatttccgttgcaatggataag
D H N A Y R C F S Q P R H I S V A M D K
tttggattcagcctaccttatgttcagtattttggaggtgtctctgctctaagtaaacaa
F G F S L P Y V Q Y F G G V S A L S K Q
cagtttctaaccatcaatggatttcctaataattattggggctggggaggagaagatgat
Q F L T I N G F P N N Y W G W G G E D D
gacatttttaacagattagtttttagaggcatgtctatatctcgcccaaatgctgtggtc
D I F N R L V F R G M S I S R P N A V V
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G R C R M I R H S R D K K N E P N P Q R
tttgaccgaattgcacacacaaaggagacaatgctctctgatggtttgaactcactcacc
F D R I A H T K E T M L S D G L N S L T
taccaggtgctggatgtacagagatacccattgtatacccaaatcacagtggacatcggg
Y Q V L D V Q R Y P L Y T Q I T V D I G
acaccgagctag
T P S -

FIG. 9

MSKRNPKILKIFLYMLLLNSLFLIIYFVFHSSSFSPEQSQPPHIYHVSVNNQSAIGQSSGELRTGGARPPPPLGASSQPRPGGDSSPVVDSG
PGPASNLTSVPVPHTTALSLPACPEESPLLVGPMLIEFNMPVDLELVAKQNPNVKMGGRYAPRDCVSPHKVAIIIPFRNRQEHLKYWLY
YLHPVLQRQQLDYGIYVINQAGDTIFNRAKLLNVGFQEALKDYDYTCFVFSDVDLIPMNDHNAYRCFSQPRHISVAMDKFGFSLPYVQ
YFGGVSALSKQQFLTINGFPNNYWGWGGEDDDIFNRLVFRGMSISRPNAVVGRCRMIRHSRDKKNEPNPQRFDRIAHTKETMLSDGLN
SLTYQVLDVQRYPLYTQITVDIGTPS

FIG. 10

CCATGGTGATGAGACGCTACAAGCTCTTTCTCATGTTCTGTATGGCCGGCCTGTGCCTCATCTCCTTCCTGCACTTCTTCAAGACC
CTGTCCTATGTCACCTTCCCCCGAGAACTGGCCTCCCTCAGCCCTAACCTGGTGTCCAGCTTTTTCTGGAACAATGCCCCGGTCAC
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GCCCTTCGCCTTCCACATGCGCAAGTCGCTCTACGGCTTCTTCTGGAAGCAGCCGGGCACCCTGGAGGTGGTGTCAGGCTGCACG
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AGCACATGTATGCGCCCAAGTACCTGCTGAAGAACTACGACCGGTTCCACTACCTGCTGGACAACCCCTACCAGGAGCCCAGGA
GCACGGCGGCGGGCGGGTGGCGCCACAGGGGTCCCGAGGGAAGGCCGCCCGCCCGGGGCAAACTGGACGAGGCGGAAGTCGAA
CAAAAACTCATCTCAGAAGAGGATCTGAATTAGGATCC

FIG. 11

```
ccatggtgatgagacgctacaagctctttctcatgttctgtatggccggcctgtgcctcatc
  M  V  M  R  R  Y  K  L  F  L  M  F  C  M  A  G  L  C  L  I
tccttcctgcacttcttcaagaccctgtcctatgtcaccttcccccgagaactggcctcc
 S  F  L  H  F  F  K  T  L  S  Y  V  T  F  P  R  E  L  A  S
ctcagccctaacctggtgtccagcttttctggaacaatgccccggtcacgccccaggcc
 L  S  P  N  L  V  S  S  F  F  W  N  N  A  P  V  T  P  Q  A
agccccgagccaggaggccctgacctgctgcgtaccccactctactcccactcgcccctg
 S  P  E  P  G  G  P  D  L  L  R  T  P  L  Y  S  H  S  P  L
ctgcagccgctgccgcccagcaaggcggccgaggagctccaccgggtggacttggtgctg
 L  Q  P  L  P  P  S  K  A  A  E  E  L  H  R  V  D  L  V  L
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 P  E  D  T  T  E  Y  F  V  R  T  K  A  G  G  V  C  F  K  P
ggcaccaagatgctggagaggccgccccgggacggccggaggagaagcctgaggggcc
 G  T  K  M  L  E  R  P  P  P  G  R  P  E  E  K  P  E  G  A
aacggctcctcggcccggcggccaccccggtacctcctgagcgcccgggagcgcacgggg
 N  G  S  S  A  R  R  P  P  R  Y  L  L  S  A  R  E  R  T  G
ggccgaggcgcccggcgcaagtgggtggagtgcgtgtgcctgcccggctggcacggaccc
 G  R  G  A  R  R  K  W  V  E  C  V  C  L  P  G  W  H  G  P
agctgcggcgtgcccactgtggtgcagtactccaacctgcccaccaaggagcggctggtg
 S  C  G  V  P  T  V  V  Q  Y  S  N  L  P  T  K  E  R  L  V
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 P  R  E  V  P  R  R  V  I  N  A  I  N  V  N  H  E  F  D  L
ctggacgtgcgcttccacgagctgggcgacgtggtggacgcctttgtggtgtgcgagtcc
 L  D  V  R  F  H  E  L  G  D  V  V  D  A  F  V  V  C  E  S
aacttcacggcttatggggagccgcggccgctcaagttccgggagatgctgaccaatggc
 N  F  T  A  Y  G  E  P  R  P  L  K  F  R  E  M  L  T  N  G
accttcgagtacatccgccacaaggtgctctatgtcttcctggaccacttcccgcccggc
 T  F  E  Y  I  R  H  K  V  L  Y  V  F  L  D  H  F  P  P  G
ggccggcaggacggctggatcgccgacgactacctgcgcaccttcctcacccaggacggc
 G  R  Q  D  G  W  I  A  D  D  Y  L  R  T  F  L  T  Q  D  G
gtctcgcggctgcgcaacctgcggcccgacgacgtcttcatcattgacgatgcggacgag
 V  S  R  L  R  N  L  R  P  D  D  V  F  I  I  D  D  A  D  E
atcccggcccgtgacggcgtccttttcctcaagctctacgatggctggaccgagcccttc
 I  P  A  R  D  G  V  L  F  L  K  L  Y  D  G  W  T  E  P  F
gccttccacatgcgcaagtcgctctacggcttcttctggaagcagccgggcaccctggag
 A  F  H  M  R  K  S  L  Y  G  F  F  W  K  Q  P  G  T  L  E
gtggtgtcaggctgcacggtggacatgctgcaggcagtgtatgggctggacggcatccgc
 V  V  S  G  C  T  V  D  M  L  Q  A  V  Y  G  L  D  G  I  R
ctgcgccgccgccagtactacaccatgcccaacttcagacagtatgagaaccgcaccggc
 L  R  R  R  Q  Y  Y  T  M  P  N  F  R  Q  Y  E  N  R  T  G
cacatcctggtgcagtggtcgctgggcagccccctgcacttcgccggctggcactgctcc
 H  I  L  V  Q  W  S  L  G  S  P  L  H  F  A  G  W  H  C  S
tggtgcttcacgcccgagggcatctacttcaagctcgtgtccgcccagaatggcgacttc
 W  C  F  T  P  E  G  I  Y  F  K  L  V  S  A  Q  N  G  D  F
ccacgctggggtgactacgaggacaagcgggacctgaactacatccgcggcctgatccgc
 P  R  W  G  D  Y  E  D  K  R  D  L  N  Y  I  R  G  L  I  R
accgggggctggttcgacggcacgcagcaggagtacccgcctgcagaccccagcgagcac
 T  G  G  W  F  D  G  T  Q  Q  E  Y  P  P  A  D  P  S  E  H
atgtatgcgcccaagtacctgctgaagaactacgaccggttccactacctgctggacaac
 M  Y  A  P  K  Y  L  L  K  N  Y  D  R  F  H  Y  L  L  D  N
ccctaccaggagcccaggagcacggcggcgggcgggtggcgccacaggggtcccgaggga
 P  Y  Q  E  P  R  S  T  A  A  G  G  W  R  H  R  G  P  E  G
aggccgcccgcccggggcaaactggacgaggcggaagtcgaacaaaaactcatctcagaa
 R  P  P  A  R  G  K  L  D  E  A  E  V  E  Q  K  L  I  S  E
gaggatctgaattaggatcc
 E  D  L  N  -  D
```

FIG. 12

MVMRRYKLFL MFCMAGLCLI SFLHFFKTLS YVTFPRELAS LSPNLVSSFF WNNAPVTPQA SPEPGGPDLL RTPLYSHSPL
LQPLPPSKAA EELHRVDLVL PEDTTEYFVR TKAGGVCFKP GTKMLERPPP GRPEEKPEGA NGSSARRPPR YLLSARERTG
GRGARRKWVE CVCLPGWHGP SCGVPTVVQY SNLPTKERLV PREVPRRVIN AINVNHEFDL LDVRFHELGD VVDAFVVCES
NFTAYGEPRP LKFREMLTNG TFEYIRHKVL YVFLDHFPPG GRQDGWIADD YLRTFLTQDG VSRLRNLRPD DVFIIDDADE
IPARDGVLFL KLYDGWTEPF AFHMRKSLYG FFWKQPGTLE VVSGCTVDML QAVYGLDGIR LRRRQYYTMP NFRQYENRTG
HILVQWSLGS PLHFAGWHCS WCFTPEGIYF KLVSAQNGDF PRWGDYEDKR DLNYIRGLIR TGGWFDGTQQ EYPPADPSEH
MYAPKYLLKN YDRFHYLLDN PYQEPRSTAA GGWRHRGPEG RPPARGKLDE AEVEQKLISE EDLN

FIG. 13

CATGAGTAAACGGAATCCGAAGATTCTGAAGATTTTTCTGTATATGTTACTTCTCAACTCTCTCTTTCTCATCATCTACTTCGTTTT
TCACTCATCGTCGTTTTCACCGGAGCAGTCACAGCCTCCTCATATATACCACGTTTCAGTGAATAACCAATCGGCACATGGAGGC
CCTGACCTGCTGCGTACCCCACTCTACTCCCACTCGCCCCTGCTGCAGCCGCTGCCGCCCAGCAAGGCGGCCGAGGAGCTCCACC
GGGTGGACTTGGTGCTGCCCGAGGACACCACCGAGTATTTCGTGCGCACCAAGGCCGGCGGCGTCTGCTTCAAACCCGGCACCA
AGATGCTGGAGAGGCCGCCCCCGGGACGGCCGGAGGAGAAGCCTGAGGGGGCCAACGGCTCCTCGGCCCGGCGGCCACCCCGG
TACCTCCTGAGCGCCCGGGAGCGCACGGGGGGCCGAGGCGCCCGGCGCAAGTGGGTGGAGTGCGTGTGCCTGCCCGGCTGGCAC
GGACCCAGCTGCGGCGTGCCCACTGTGGTGCAGTACTCCAACCTGCCCACCAAGGAGCGGCTGGTGCCCAGGGAGGTGCCGCGC
CGCGTCATCAACGCCATCAACGTCAACCACGAGTTCGACCTGCTGGACGTGCGCTTCCACGAGCTGGGCGACGTGGTGGACGCCT
TTGTGGTGTGCGAGTCCAACTTCACGGCTTATGGGGAGCCGCGGCCGCTCAAGTTCCGGGAGATGCTGACCAATGGCACCTTCGA
GTACATCCGCCACAAGGTGCTCTATGTCTTCCTGGACCACTTCCCGCCCGGCGGCCGGCAGGACGGCTGGATCGCCGACGACTAC
CTGCGCACCTTCCTCACCCAGGACGGCGTCTCGCGGCTGCGCAACCTGCGGCCCGACGACGTCTTCATCATTGACGATGCGGACG
AGATCCCGGCCCGTGACGGCGTCCTTTTCCTCAAGCTCTACGATGGCTGGACCGAGCCCTTCGCCTTCCACATGCGCAAGTCGCT
CTACGGCTTCTTCTGGAAGCAGCCGGGCACCCTGGAGGTGGTGTCAGGCTGCACGGTGGACATGCTGCAGGCAGTGTATGGGCT
GGACGGCATCCGCCTGCGCCGCCGCCAGTACTACACCATGCCCAACTTCAGACAGTATGAGAACCGCACCGGCCACATCCTGGT
GCAGTGGTCGCTGGGCAGCCCCCTGCACTTCGCCGGCTGGCACTGCTCCTGGTGCTTCACGCCCGAGGGCATCTACTTCAAGCTC
GTGTCCGCCCAGAATGGCGACTTCCCACGCTGGGGTGACTACGAGGACAAGCGGGACCTGAACTACATCCGCGGCCTGATCCGC
ACCGGGGGCTGGTTCGACGGCACGCAGCAGGAGTACCCGCCTGCAGACCCCAGCGAGCACATGTATGCGCCCAAGTACCTGCTG
AAGAACTACGACCGGTTCCACTACCTGCTGGACAACCCCTACCAGGAGCCCAGGAGCACGGCGGCGGGCGGGTGGCGCCACAG
GGGTCCCGAGGGAAGGCCGCCCGCCCGGGGCAAACTGGACGAGGCGGAAGTCGAACAAAAACTCATCTCAGAAGAGGATCTGA
ATTAGGATCC

FIG. 14

catgagtaaacggaatccgaagattctgaagatttttctgtatatgttacttctcaactct
M S K R N P K I L K I F L Y M L L L N S
ctctttctcatcatctacttcgtttttcactcatcgtcgttttcaccggagcagtcacag
L F L I I Y F V F H S S S F S P E Q S Q
cctcctcatatataccacgtttcagtgaataaccaatcggcacatggaggccctgacctg
P P H I Y H V S V N N Q S A H G G P D L
ctgcgtaccccactctactcccactcgcccctgctgcagccgctgccgcccagcaaggcg
L R T P L Y S H S P L L Q P L P P S K A
gccgaggagctccaccgggtggacttggtgctgcccgaggacaccaccgagtatttcgtg
A E E L H R V D L V L P E D T T E Y F V
cgcaccaaggccggcggcgtctgcttcaaacccggcaccaagatgctggagaggccgccc
R T K A G G V C F K P S T K M L E R P P
ccgggacggccggaggagaagcctgagggggccaacggctcctcggcccggcggccaccc
P G R P E E K P E G A N G S S A R R P P
cggtacctcctgagcgcccgggagcgcacgggggggccgaggcgcccggcgcaagtgggtg
R Y L L S A R E R T G G R G A R R K W V
gagtgcgtgtgcctgcccggctggcacggacccagctgcggcgtgcccactgtggtgcag
E C V C L P G W H G P S C G V P T V V Q
tactccaacctgcccaccaaggagcggctggtgcccagggaggtgccgcgccgcgtcatc
Y S N L P T K E R L V P R E V P R R V I
aacgccatcaacgtcaaccacgagttcgacctgctggacgtgcgcttccacgagctgggc
N A I N V N H E F D L L D V R F H E L G
gacgtggtggacgcctttgtggtgtgcgagtccaacttcacggcttatggggagccgcgg
D V V D A F V V C E S N F T A Y G E P R
ccgctcaagttccgggagatgctgaccaatggcaccttcgagtacatccgccacaaggtg
P L K F R E M L T N G T F E Y I R H K V
ctctatgtcttcctggaccacttcccgcccggcggccggcaggacggctggatcgccgac
L Y V F L D H F P P G G R Q D G W I A D
gactacctgcgcaccttcctcacccaggacggcgtctcgcggctgcgcaacctgcggccc
D Y L R T F L T Q D G V S R L R N L R P
gacgacgtcttcatcattgacgatgcggacgagatcccggcccgtgacggcgtccttttc
D D V F I I D D A D E I P A R D G V L F
Ctcaagctctacgatggctggaccgagcccttcgccttccacatgcgcaagtcgctctac
L K L Y D G W T E P F A F H M R K S L Y
ggcttcttctggaagcagccgggcaccctggaggtggtgtcaggctgcacggtggacatg
G F F W K Q P G T L E V V S G C T V D M
ctgcaggcagtgtatgggctggacggcatccgcctgcgccgccgccagtactacaccatg
L Q A V Y G L D G I R L R R R Q Y Y T M
cccaacttcagacagtatgagaaccgcaccggccacatcctggtgcagtggtcgctgggc
P N F R Q Y E N R T G H I L V Q W S L G
agccccctgcacttcgccggctggcactgctcctggtgcttcacgcccgagggcatctac
S P L H F A G W H C S W C F T P E G I Y
ttcaagctcgtgtccgcccagaatggcgacttcccacgctggggtgactacgaggacaag
F K L V S A Q N G D F P R W G D Y E D K
cgggacctgaactacatccgcggcctgatccgcaccgggggctggttcgacggcacgcag
R D L N Y I R G L I R T G G W F D G T Q
caggagtacccgcctgcagaccccagcgagcacatgtatgcgcccaagtacctgctgaag
Q E Y P P A D P S E H M Y A P K Y L L K
aactacgaccggttccactacctgctggacaacccctaccaggagcccaggagcacggcg
N Y D R F H Y L L D N P Y Q E P R S T A
gcgggcgggtggcgccacaggggtcccgagggaaggccgcccgcccggggcaaactggac
A G G W R H R G P E G R P P A R G K L D
gaggcggaagtcgaacaaaaactcatctcagaagaggatctgaattaggatcc
E A E V E Q K L I S E E D L N - D

FIG. 15

MSKRNPKILK IFLYMLLLNS LFLIIYFVFH SSSFSPEQSQ PPHIYHVSVN NQSAHGGPDL LRTPLYSHSP LLQPLPPSKA
AEELHRVDLV LPEDTTEYFV RTKAGGVCFK PGTKMLERPP PGRPEEKPEG ANGSSARRPP RYLLSARERT GGRGARRKWV
ECVCLPGWHG PSCGVPTVVQ YSNLPTKERL VPREVPRRVI NAINVNHEFD LLDVRFHELG DVVDAFVVCE SNFTAYGEPR
PLKFREMLTN GTFEYIRHKV LYVFLDHFPP GGRQDGWIAD DYLRTFLTQD GVSRLRNLRP DDVFIIDDAD EIPARDGVLF
LKLYDGWTEP FAFHMRKSLY GFFWKQPGTL EVVSGCTVDM LQAVYGLDGI RLRRRQYYTM PNFRQYENRT GHILVQWSLG
SPLHFAGWHC SWCFTPEGIY FKLVSAQNGD FPRWGDYEDK RDLNYIRGLI RTGGWFDGTQ QEYPPADPSE HMYAPKYLLK
NYDRFHYLLD NPYQEPRSTA AGGWRHRGPE GRPPARGKLD EAEVEQKLIS EEDLN

FIG. 16

GGCGCGCCTCGAGGCGATCGCAGATCTAATCTAACCAATTACGATACGCTTTGGGTACACTTGATTTTTGTTTCAG
TGGTTACATATATCTTGTTTTATATGCTATCTTTAAGGATCTGCACAAAGATTATTTGTTGATGTTCTTGATGGGG
CTCAGAAGATTTGATATGATACACTCTAATCTTTAGGAGATACCAGCCAGGATTATATTCAGTAAGACAATCAAAT
TTTACGTGTTCAAACTCGTTATCTTTTCATTCAAAGGATGAGCCAGAATCTTTATAGAATGATTGCAATCGAGAAT
ATGTTCGGCCGATATGCCTTTGTTGGCTTCAATATTCTACATATCACACAAGAATCGACCGTATTGTACCCTCTTT
CCATAAAGGAAAACACAATATGCAGATGCTTTTTTCCCACATGCAGTAACATATAGGTATTCAAAAATGGCTAAAA
GAAGTTGGATAACAAATTGACAACTATTTCCATTTCTGTTATATAAATTTCACAACACACAAAAGCCCGTAATCAA
GAGTCTGCCCATGTACGAAATAACTTCTATTATTTGGTATTGGGCCTAAGCCCAGCTCAGAGTACGTGGGGGTACC
ACATATAGGAAGGTAACAAAATACTGCAAGATAGCCCCATAACGTACCAGCCTCTCCTTACCACGAAGAGATAAGA
TATAAGACCCACCCTGCCACGTGTCACATCGTCATGGTGGTTAATGATAAGGGATTACATCCTTCTATGTTTGTGG
ACATGATGCATGTAATGTCATGAGCCACAGGATCCAATGGCCACAGGAACGTAAGAATGTAGATAGATTTGATTTT
GTCCGTTAGATAGCAAACAACATTATAAAAGGTGTGTATCAATAGGAACTAATTCACTCATTGGATTCATAGAAGT
CCATTCCTCCTAAGTATCTAGAAACCATGGCGAGGATCTCGTGTGACTTGAGATTTCTTCTCATCCCGGCAGCTTT
CATGTTCATCTACATCCAGATGAGGCTTTTCCAGACGCAATCACAGTATGCAGATCGCCTCAGTTCCGCTATCGAA
TCTGAGAACCATTGCACTAGTCAAATGCGAGGCCTCATAGATGAAGTTAGCATCAAACAGTCGCGGATTGTTGCCC
TCGAAGATATGAAGAACCGCCAGGACGAAGAACTTGTGCAGCTTAAGGATCTAATCCAGACGTTTGAAAAAAAAGG
AATAGCAAAACTCACTCAAGGTGGAGCCATGGATTCCAATTCAGGCGCCGTCGTTGATATCACAACTAAAGATCTA
TACGATAGGATTGAGTTTCTTGATACAGATGGTGGTCCATGGAAACAAGGTTGGAGAGTTACGTATAAAGACGATG
AGTGGGAGAAAGAGAAGCTCAAAATCTTCGTTGTTCCTCATTCTCATAACGATCCTGGTTGGAAATTGACTGTAGA
GGAGTATTATCAGAGACAATCCAGACATATTCTTGACACCATTGTTGAGACTTTATCTAAGGTATGACGAAAGTTT
TTGCTTTTGGTTTTAATATTTTAATTCTCTCCCATGGTTATCCCGTGAACAATCTTAAATGTCTTAAAATTCTCAT
GACGTCATTAAACTCTATAACCAAACTTCTTTGCTGGGTTCTGTTTTTTTTTAGTTTCGTGATGAAACAGAGTTCT
AGAAGTTCGTTCTTTTGGAAAATTTGAAGTCTTTGGAGCTAAAGTTTGTTTTTTTATTACTGGGTTTTGAGATTGA
AGGATAGCTAGAATCTTATTTGTGTGGGGGTTTGTTTTGAATATGTTTAATAGGATTCAAGAAGAAAGTTTATATG
GGAGGAGATGTCATATCTGGAGAGATGGTGGAGAGACGCTTCACCTAATAAACAAGAAGCTTTGACTAAATTGGTT

FIG. 17

AAGGATGGGCAGCTAGAGATTGTTGGAGGTGGCTGGGTTATGAATGATGAGGCTAATTCACATTATTTTGCCATAA
TTGAACAGATAGCAGAGGGTAATATGTGGCTGAATGACACAATTGGGGTTATTCCTAAGAATTCTTGGGCTATAGA
TCCCTTTGGCTATTCATCAACCATGGCTTATCTTCTCCGGCGTATGGGTTTTGAAAACATGCTTATTCAAAGGACT
CATTACGAGCTCAAGAAAGACCTTGCCCAGCATAAGAATCTTGAATATATTTGGCGTCAGAGCTGGGATGCTATGG
AAACCACAGATATCTTTGTTCATATGATGCCGTTTTATTCATACGATATCCCACACACTTGTGGACCAGAGCCTGC
AATTTGCTGTCAGTTTGATTTCGCTCGGATGCGGGGATTTAAGTATGAACTTTGTCCATGGGGAAAGCACCCAGTG
GAGACCACACTAGAAAATGTGCAGGAGAGGGCATTAAAGCTTCTGGATCAATACAGGAAAAAATCCACTCTATATC
GAACTAATACACTTCTTATACCTCTTGGAGATGATTTTAGGTACATTAGTATCGATGAAGCCGAGGCTCAGTTCCG
TAACTACCAGATGTTGTTTGATCACATCAACTCTAATCCTAGTCTAAACGCAGAAGCAAAGTTTGGTACTTTGGAG
GATTATTTCAGAACAGTCCGAGAAGAAGCAGACAGAGTGAATTATTCTCGTCCTGGTGAGGTTGGCTCTGGTCAGG
TTGTTGGTTTCCCTTCTCTGTCAGGTGACTTCTTTACATATGCAGATAGGCAACAAGACTATTGGAGTGGTTATTA
TGTTTCAAGACCTTTCTTCAAAGCTGTTGATCGTGTGCTCGAGCATACCCTTCGTGGAGCTGAGATCATGATGTCA
TTTCTGCTAGGTTATTGCCATCGAATTCAATGTGAGAAATTTCCAACAAGTTTTACGTATAAGTTGACTGCTGCAA
GAAGAAATCTGGCTCTTTTCCAGCACCATGATGGGGTAACTGGAACTGCTAAGGATTATGTGGTACAAGATTACGG
CACCCGGATGCATACTTCATTGCAAGACCTTCAGATCTTTATGTCTAAAGCAATCGAAGTTCTTCTTGGGATCCGC
CACGAGAAAGAAAAATCTGATCAATCCCCATCATTTTTCGAGGCAGAGCAAATGAGATCAAAGTATGATGCTCGGC
CAGTTCACAAGCCAATTGCTGCCCGGGAAGGAAATTCGCACACAGTTATACTCTTCAATCCATCAGAACAGACGAG
AGAGGAGGTGGTGACGGTTGTTGTTAACCGCGCTGAAATCTCGGTTTTGGACTCAAACTGGACTTGTGTCCCTAGC
CAAATTTCTCCTGAAGTGCAGCATGACGATACCAAACTATTCACCGGCAGACATCGCCTTTACTGGAAAGCTTCCA
TCCCAGCTCTTGGTCTGAGAACATATTTCATTGCTAATGGGAATGTCGAGTGTGAGAAAGCTACTCCGTCTAAACT
CAAATACGCTTCTGAGTTTGACCCATTTCCTTGTCCTCCTCCATATTCCTGCTCCAAACTGGACAACGACGTTACT
GAGATCCGAAATGAACATCAGACTCTTGTGTTTGATGTGAAGAACGGATCACTGCGGAAGATAGTCCATAGAAACG
GATCAGAGACTGTTGTGGGAGAAGAGATAGGTATGTACTCTAGTCCAGAGAGTGGAGCTTACCTGTTCAAACCAGA
TGGTGAAGCTCAGCCAATTGTTCAACCTGATGGACATGTAGTCACCTCTGAGGGTCTGCTGGTTCAAGAAGTCTTC
TCTTACCCTAAAACCAAATGGGAGAAATCACCCCTCTCTCAGAAAACTCGTCTTTACACTGGAGGTAATACGCTTC
AGGATCAAGTGGTCGAGATAGAATATCATGTTGAGCTTCTTGGTAATGATTTTGATGACCGGGAATTGATTGTCCG
GTACAAGACTGATGTTGACAACAAGAAGGTCTTCTATTCAGATCTCAATGGTTTCCAAATGAGCAGGAGAGAAACT

FIG. 17 Cont.

TATGATAAGATCCCTCTTCAAGGAAACTACTACCCAATGCCATCTCTCGCATTTATCCAAGGATCCAATGGTCAGA
GATTCTCCGTGCACTCTCGTCAATCTCTCGGTGTTGCAAGCCTCAAAGAGGGTTGGTTGGAGATTATGCTGGACAG
ACGGTTGGTTCGTGATGACGGACGGGGTCTAGGGCAAGGTGTGATGGATAACCGCGCAATGACCGTGGTATTTCAC
CTTCTTGCGGAATCTAACATTTCTCAAGCAGACCCTGCTTCCAACACTAACCCGAGGAACCCTTCGCTTCTCTCTC
ACCTCATAGGTGCTCACTTAAACTACCCCATAAACACATTCATTGCCAAGAAACCGCAAGACATATCTGTGCGTGT
TCCACAATACGGTTCCTTTGCTCCTTTAGCCAAACCGTTACCATGTGACCTCCACATTGTAAATTTCAAGGTTCCT
CGTCCATCCAAATACTCTCAGCAATTGGAAGAAGACAAGCCAAGGTTCGCTCTTATCCTCAATAGACGAGCTTGGG
ATTCAGCTTATTGCCATAAAGGAAGACAAGTAAACTGCACAAGCATGGCTAATGAACCAGTAAACTTTTCCGACAT
GTTCAAAGATCTTGCAGCTTCAAAGGTAAAACCAACTTCACTGAATCTCTTGCAAGAAGATATGGAGATTCTTGGG
TACGATGACCAAGAGCTACCTCGAGATAGTTCACAGCCACGGGAAGGACGTGTCTCGATCTCTCCCATGGAAATAC
GAGCTTATAAGCTTGAACTGCGACCTCACAAGTGAACCTGCTGAAGATCCGCTAGAGTCCGCAAAAATCACCAGTC
TCTCTCTACAAATCTATCTCTCTCTATTTTTCTCCAGAATAATGTGTGAGTAGTTCCCAGATAAGGGAATTAGGGT
TCTTATAGGGTTTCGCTCATGTGTTGAGCATATAAGAAACCCTTAGTATGTATTTGTATTTGTAAAATACTTCTAT
CAATAAAATTTCTAATCCTAAAACCAAAATCCCGCGCGCGCCTCGAGGCGATCGCAGATCTCATTATACCGTTAGA
AGCATAGTTAAAATCTAAAGCTTGTCGTTAATTCTAGTCATTTTACATTGTTGGGTTCTACATTATTAATGAATTT
TCTAATGCAAATACAGAATTTAAATCAAAATTGTTGAATTATGCTAAACATGTAACATACGTATATCTCCGCCTTG
TGTGTTGTATTAACTTGAAGTTATCATAAGAACCACAAATACACTAGTAAATCTATGAGAAGGCAGGTGGCAACAC
AAACAAGAGTATCTAAGATTTTCATTTGTGACTATAGGAATATAATATCTCTTATCTGATTTAATGAATCCACATG
TTCACTTCTCATTTGTCCACAAGATCACAACTTTATCTTCAATATTCACAACTTGTTATATCCACCACAATTTCAT
TCTTTTCACTTAGCCCCACAAAATACTTTGTCCCCTTATTTGCCACCTTTTGTATTTAATTTATTCTTGTGGAGCT
AAGTGTTCATATTATTCTTCTTCTCAAAAAAACAAAAACAAAAAAAAAAGAGAAGAAAACCATGGCGAGGATCTCGT
GTGACTTGAGATTTCTTCTCATCCCGGCAGCTTTCATGTTCATCTACATCCAGATGAGGCTTTTCCAGACGCAATC
ACAGTATGCAGATCGCCTCAGTTCCGCTATCGAATCTGAGAACCATTGCACTAGTCAAATGCGAGGCCTCATAGAT
GAAGTTAGCATCAAACAGTCGCGGATTGTTGCCCTCGAAGATATGAAGAACCGCCAGGACGAAGAACTTGTGCAGC
TTAAGGATCTAATCCAGACGTTTGAAAAAAAAGGAATAGCAAAACTCACTCAAGGTGGAGCCATGGCTCTAAGGTT
GCATAGAAGGAACCATTTTTCGCCTAGAAATACGGATCTGTTCCCGGATTTGGCAAAAGATCGTGTGGTTATCGTC
TTGTATGTGCATAATCGGGCTCAGTATTTTCGAGTCACAGTGGAAAGTTTGTCGAAGGTTAAAGGTATAAGTGAGA
CATTGTTGATTGTTAGTCATGATGGTTACTTTGAAGAGATGAATAGGATTGTGGAGAGTATTAAGTTTTGTCAAGT

FIG. 17 Cont.

GAAACAGATTTTCTCGCCTTATTCGCCTCATATATATCGTACTAGCTTCCCGGGTGTGACCCTGAATGATTGTAAG
AACAAGGGTGATGAGGCAAAGGGGCATTGTGAAGGTAATCCTGATCAGTATGGGAATCATCGGTCTCCGAAGATTG
TATCTTTGAAGCATCACTGGTGGTGGATGATGAACACTGTATGGGATGGGTTGGAAGAGACTAAAGGACATGAGGG
GCATATCCTTTTCATTGAAGAAGATCATTTTCTGTTTCCTAATGCCTATCGTAACATACAGACTCTTACGAGGCTG
AAACCCGCAAAGTGTCCTGACTGTTTTGCTGCTAATTTAGCACCGTCTGATGTGAAGTCAAGAGGAGAAGGGCTTG
AAAGTTTGGTTGCAGAGAGAATGGGAAATGTTGGGTATTCTTTTAATAGAAGTGTGTGGGAGAATATTCATCAGAA
GGCAAGAGAGTTTTGTTTCTTTGATGATTACAACTGGGATATAACGATGTGGGCAACGGTTTTCCCGTCGTTTGGT
TCCCCGGTGTACACATTGCGAGGGCCTAGGACTAGTGCGGTACACTTTGGAAAATGTGGGTTGCATCAAGGTAGAG
GAGATGAGGGTGATTGCATCGATAATGGGGTCGTAAACATAGAAGTTAAGGAAACAGATAAAGTTGTGAACATAAA
AGAAGGATGGGGAGTTCGGGTGTATAAGCATCAAGCGGGTTATAAAGCCGGTTTCGAAGGTTGGGGAGGTTGGGGC
GATGATAGGGACCGACATTTATGTTTGGATTTTGCCACTATGTATCGTTACAGCAGTAGCAGTGCATCTCCATGAA
ACGGATCCGCTAGAGTCCGCAAAAATCACCAGTCTCTCTCTACAAATCTATCTCTCTCTATTTTTCTCCAGAATAA
TGTGTGAGTAGTTCCCAGATAAGGGAATTAGGGTTCTTATAGGGTTTCGCTCATGTGTTGAGCATATAAGAAACCC
TTAGTATGTATTTGTATTTGTAAAATACTTCTATCAATAAAATTTCTAATCCTAAAACCAAAATCCCGCGAGAGAC
CTCTTAATTAA

FIG. 17 Cont.

GGCGCGCCTCGAGGCGATCGCAGATCTAATCTAACCAATTACGATACGCTTTGGGTACACTTGATTTTTGTTTCAG
TGGTTACATATATCTTGTTTTATATGCTATCTTTAAGGATCTGCACAAAGATTATTTGTTGATGTTCTTGATGGGG
CTCAGAAGATTTGATATGATACACTCTAATCTTTAGGAGATACCAGCCAGGATTATATTCAGTAAGACAATCAAAT
TTTACGTGTTCAAACTCGTTATCTTTTCATTCAAAGGATGAGCCAGAATCTTTATAGAATGATTGCAATCGAGAAT
ATGTTCGGCCGATATGCCTTTGTTGGCTTCAATATTCTACATATCACACAAGAATCGACCGTATTGTACCCTCTTT
CCATAAAGGAAAACACAATATGCAGATGCTTTTTTCCCACATGCAGTAACATATAGGTATTCAAAAATGGCTAAAA
GAAGTTGGATAACAAATTGACAACTATTTCCATTTCTGTTATATAAATTTCACAACACACAAAAGCCCGTAATCAA
GAGTCTGCCCATGTACGAAATAACTTCTATTATTTGGTATTGGGCCTAAGCCCAGCTCAGAGTACGTGGGGGTACC
ACATATAGGAAGGTAACAAAATACTGCAAGATAGCCCCATAACGTACCAGCCTCTCCTTACCACGAAGAGATAAGA
TATAAGACCCACCCTGCCACGTGTCACATCGTCATGGTGGTTAATGATAAGGGATTACATCCTTCTATGTTTGTGG
ACATGATGCATGTAATGTCATGAGCCACAGGATCCAATGGCCACAGGAACGTAAGAATGTAGATAGATTTGATTTT
GTCCGTTAGATAGCAAACAACATTATAAAAGGTGTGTATCAATAGGAACTAATTCACTCATTGGATTCATAGAAGT
CCATTCCTCCTAAGTATCTAGAAACCATGGCGAGGATCTCGTGTGACTTGAGATTTCTTCTCATCCCGGCAGCTTT
CATGTTCATCTACATCCAGATGAGGCTTTTCCAGACGCAATCACAGTATGCAGATCGCCTCAGTTCCGCTATCGAA
TCTGAGAACCATTGCACTAGTCAAATGCGAGGCCTCATAGATGAAGTTAGCATCAAACAGTCGCGGATTGTTGCCC
TCGAAGATATGAAGAACCGCCAGGACGAAGAACTTGTGCAGCTTAAGGATCTAATCCAGACGTTTGAAAAAAAAGG
AATAGCAAAACTCACTCAAGGTGGAGCCATGGATTCCAATTCAGGCGCCGTCGTTGATATCACAACTAAAGATCTA
TACGATAGGATTGAGTTTCTTGATACAGATGGTGGTCCATGGAAACAAGGTTGGAGAGTTACGTATAAAGACGATG
AGTGGGAGAAAGAGAAGCTCAAAATCTTCGTTGTTCCTCATTCTCATAACGATCCTGGTTGGAAATTGACTGTAGA
GGAGTATTATCAGAGACAATCCAGACATATTCTTGACACCATTGTTGAGACTTTATCTAAGGTATGACGAAAGTTT
TTGCTTTTGGTTTTAATATTTTAATTCTCTCCCATGGTTATCCCGTGAACAATCTTAAATGTCTTAAAATTCTCAT
GACGTCATTAAACTCTATAACCAAACTTCTTTGCTGGGTTCTGTTTTTTTTTAGTTTCGTGATGAAACAGAGTTCT
AGAAGTTCGTTCTTTTGGAAAATTTGAAGTCTTTGGAGCTAAAGTTTGTTTTTTTATTACTGGGTTTTGAGATTGA
AGGATAGCTAGAATCTTATTTGTGTGGGGGTTTGTTTTGAATATGTTTAATAGGATTCAAGAAGAAAGTTTATATG
GGAGGAGATGTCATATCTGGAGAGATGGTGGAGAGACGCTTCACCTAATAAACAAGAAGCTTTGACTAAATTGGTT
AAGGATGGGCAGCTAGAGATTGTTGGAGGTGGCTGGGTTATGAATGATGAGGCTAATTCACATTATTTTGCCATAA

FIG. 18

TTGAACAGATAGCAGAGGGTAATATGTGGCTGAATGACACAATTGGGGTTATTCCTAAGAATTCTTGGGCTATAGA
TCCCTTTGGCTATTCATCAACCATGGCTTATCTTCTCCGGCGTATGGGTTTTGAAAACATGCTTATTCAAAGGACT
CATTACGAGCTCAAGAAAGACCTTGCCCAGCATAAGAATCTTGAATATATTTGGCGTCAGAGCTGGGATGCTATGG
AAACCACAGATATCTTTGTTCATATGATGCCGTTTTATTCATACGATATCCCACACACTTGTGGACCAGAGCCTGC
AATTTGCTGTCAGTTTGATTTCGCTCGGATGCGGGGATTTAAGTATGAACTTTGTCCATGGGGAAAGCACCCAGTG
GAGACCACACTAGAAAATGTGCAGGAGAGGGCATTAAAGCTTCTGGATCAATACAGGAAAAAATCCACTCTATATC
GAACTAATACACTTCTTATACCTCTTGGAGATGATTTTAGGTACATTAGTATCGATGAAGCCGAGGCTCAGTTCCG
TAACTACCAGATGTTGTTTGATCACATCAACTCTAATCCTAGTCTAAACGCAGAAGCAAAGTTTGGTACTTTGGAG
GATTATTTCAGAACAGTCCGAGAAGAAGCAGACAGAGTGAATTATTCTCGTCCTGGTGAGGTTGGCTCTGGTCAGG
TTGTTGGTTTCCCTTCTCTGTCAGGTGACTTCTTTACATATGCAGATAGGCAACAAGACTATTGGAGTGGTTATTA
TGTTTCAAGACCTTTCTTCAAAGCTGTTGATCGTGTGCTCGAGCATACCCTTCGTGGAGCTGAGATCATGATGTCA
TTTCTGCTAGGTTATTGCCATCGAATTCAATGTGAGAAATTTCCAACAAGTTTTACGTATAAGTTGA[illegible]GCTGCAA
GAAGAAATCTGGCTCTTTTCCAGCACCATGATGGGGTAACTGGAACTGCTAAGGATTATGTGGTACAAGATTACGG
CACCCGGATGCATACTTCATTGCAAGACCTTCAGATCTTTATGTCTAAAGCAATCGAAGTTCTTCTTGGGATCCGC
CACGAGAAAGAAAAATCTGATCAATCCCCATCATTTTTCGAGGCAGAGCAAATGAGATCAAAGTATGATGCTCGGC
CAGTTCACAAGCCAATTGCTGCCCGGGAAGGAAATTCGCACACAGTTATACTCTTCAATCCATCAGAACAGACGAG
AGAGGAGGTGGTGACGGTTGTTGTTAACCGCGCTGAAATCTCGGTTTTGGACTCAAACTGGACTTGTGTCCCTAGC
CAAATTTCTCCTGAAGTGCAGCATGACGATACCAAACTATTCACCGGCAGACATCGCCTTTACTGGAAAGCTTCCA
TCCCAGCTCTTGGTCTGAGAACATATTTCATTGCTAATGGGAATGTCGAGTGTGAGAAAGCTACTCCGTCTAAACT
CAAATACGCTTCTGAGTTTGACCCATTTCCTTGTCCTCCTCCATATTCCTGCTCCAAACTGGACAACGACGTTACT
GAGATCCGAAATGAACATCAGACTCTTGTGTTTGATGTGAAGAACGGATCACTGCGGAAGATAGTCCATAGAAACG
GATCAGAGACTGTTGTGGGAGAAGAGATAGGTATGTACTCTAGTCCAGAGAGTGGAGCTTACCTGTTCAAACCAGA
TGGTGAAGCTCAGCCAATTGTTCAACCTGATGGACATGTAGTCACCTCTGAGGGTCTGCTGGTTCAAGAAGTCTTC
TCTTACCCTAAAACCAAATGGGAGAAATCACCCCTCTCTCAGAAAACTCGTCTTTACACTGGAGGTAATACGCTTC
AGGATCAAGTGGTCGAGATAGAATATCATGTTGAGCTTCTTGGTAATGATTTTGATGACCGGGAATTGATTGTCCG
GTACAAGACTGATGTTGACAACAAGAAGGTCTTCTATTCAGATCTCAATGGTTTCCAAATGAGCAGGAGAGAAACT
TATGATAAGATCCCTCTTCAAGGAAACTACTACCCAATGCCATCTCTCGCATTTATCCAAGGATCCAATGGTCAGA

FIG. 18 Cont.

GATTCTCCGTGCACTCTCGTCAATCTCTCGGTGTTGCAAGCCTCAAAGAGGGTTGGTTGGAGATTATGCTGGACAG
ACGGTTGGTTCGTGATGACGGACGGGGTCTAGGGCAAGGTGTGATGGATAACCGCGCAATGACCGTGGTATTTCAC
CTTCTTGCGGAATCTAACATTTCTCAAGCAGACCCTGCTTCCAACACTAACCCGAGGAACCCTTCGCTTCTCTCTC
ACCTCATAGGTGCTCACTTAAACTACCCCATAAACACATTCATTGCCAAGAAACCGCAAGACATATCTGTGCGTGT
TCCACAATACGGTTCCTTTGCTCCTTTAGCCAAACCGTTACCATGTGACCTCCACATTGTAAATTTCAAGGTTCCT
CGTCCATCCAAATACTCTCAGCAATTGGAAGAAGACAAGCCAAGGTTCGCTCTTATCCTCAATAGACGAGCTTGGG
ATTCAGCTTATTGCCATAAAGGAAGACAAGTAAACTGCACAAGCATGGCTAATGAACCAGTAAACTTTTCCGACAT
GTTCAAAGATCTTGCAGCTTCAAAGGTAAAACCAACTTCACTGAATCTCTTGCAAGAAGATATGGAGATTCTTGGG
TACGATGACCAAGAGCTACCTCGAGATAGTTCACAGCCACGGGAAGGACGTGTCTCGATCTCTCCCATGGAAATAC
GAGCTTATAAGCTTGAACTGCGACCTCACAAGTGAACCTGCTGAAGATCCGCTAGAGTCCGCAAAAATCACCAGTC
TCTCTCTACAAATCTATCTCTCTCTATTTTTCTCCAGAATAATGTGTGAGTAGTTCCCAGATAAGGGAATTAGGGT
TCTTATAGGGTTTCGCTCATGTGTTGAGCATATAAGAAACCCTTAGTATGTATTTGTATTTGTAAAATACTTCTAT
CAATAAAATTTCTAATCCTAAAACCAAAATCCCGCGAGAGACCTCTTAATTAA

FIG. 18 Cont.

CCATGGCGAGGATCTCGTGTGACTTGAGATTTCTTCTCATCCCGGCAGCTTTCATGTTCATCTACATCCAGATGAG
GCTTTTCCAGACGCAATCACAGTATGCAGATCGCCTCAGTTCCGCTATCGAATCTGAGAACCATTGCACTAGTCAA
ATGCGAGGCCTCATAGATGAAGTTAGCATCAAACAGTCGCGGATTGTTGCCCTCGAAGATATGAAGAACCGCCAGG
ACGAAGAACTTGTGCAGCTTAAGGATCTAATCCAGACGTTTGAAAAAAAAAGGAATAGCAAAACTCACTCAAGGTGG
AGCCATGGATTCCAATTCAGGCGCCGTCGTTGATATCACAACTAAAGATCTATACGATAGGATTGAGTTTCTTGAT
ACAGATGGTGGTCCATGGAAACAAGGTTGGAGAGTTACGTATAAAGACGATGAGTGGGAGAAAGAGAAGCTCAAAA
TCTTCGTTGTTCCTCATTCTCATAACGATCCTGGTTGGAAATTGACTGTAGAGGAGTATTATCAGAGACAATCCAG
ACATATTCTTGACACCATTGTTGAGACTTTATCTAAGGTATGACGAAAGTTTTTGCTTTTGGTTTTAATATTTTAA
TTCTCTCCCATGGTTATCCCGTGAACAATCTTAAATGTCTTAAAATTCTCATGACGTCATTAAACTCTATAACCAA
ACTTCTTTGCTGGGTTCTGTTTTTTTTTAGTTTCGTGATGAAACAGAGTTCTAGAAGTTCGTTCTTTTGGAAAATT
TGAAGTCTTTGGAGCTAAAGTTTGTTTTTTTATTACTGGGTTTTGAGATTGAAGGATAGCTAGAATCTTATTTGTG
TGGGGGTTTGTTTTGAATATGTTTAATAGGATTCAAGAAGAAAGTTTATATGGGAGGAGATGTCATATCTGGAGAG
ATGGTGGAGAGACGCTTCACCTAATAAACAAGAAGCTTTGACTAAATTGGTTAAGGATGGGCAGCTAGAGATTGTT
GGAGGTGGCTGGGTTATGAATGATGAGGCTAATTCACATTATTTTGCCATAATTGAACAGATAGCAGAGGGTAATA
TGTGGCTGAATGACACAATTGGGGTTATTCCTAAGAATTCTTGGGCTATAGATCCCTTTGGCTATTCATCAACCAT
GGCTTATCTTCTCCGGCGTATGGGTTTTGAAAACATGCTTATTCAAAGGACTCATTACGAGCTCAAGAAAGACCTT
GCCCAGCATAAGAATCTTGAATATATTTGGCGTCAGAGCTGGGATGCTATGGAAACCACAGATATCTTTGTTCATA
TGATGCCGTTTTATTCATACGATATCCCACACACTTGTGGACCAGAGCCTGCAATTTGCTGTCAGTTTGATTTCGC
TCGGATGCGGGGATTTAAGTATGAACTTTGTCCATGGGGAAAGCACCCAGTGGAGACCACACTAGAAAATGTGCAG
GAGAGGGCATTAAAGCTTCTGGATCAATACAGGAAAAAATCCACTCTATATCGAACTAATACACTTCTTATACCTC
TTGGAGATGATTTTAGGTACATTAGTATCGATGAAGCCGAGGCTCAGTTCCGTAACTACCAGATGTTGTTTGATCA
CATCAACTCTAATCCTAGTCTAAACGCAGAAGCAAAGTTTGGTACTTTGGAGGATTATTTCAGAACAGTCCGAGAA
GAAGCAGACAGAGTGAATTATTCTCGTCCTGGTGAGGTTGGCTCTGGTCAGGTTGTTGGTTTCCCTTCTCTGTCAG
GTGACTTCTTTACATATGCAGATAGGCAACAAGACTATTGGAGTGGTTATTATGTTTCAAGACCTTTCTTCAAAGC
TGTTGATCGTGTGCTCGAGCATACCCTTCGTGGAGCTGAGATCATGATGTCATTTCTGCTAGGTTATTGCCATCGA
ATTCAATGTGAGAAATTTCCAACAAGTTTTACGTATAAGTTGACTGCTGCAAGAAGAAATCTGGCTCTTTTCCAGC

FIG. 19

ACCATGATGGGGTAACTGGAACTGCTAAGGATTATGTGGTACAAGATTACGGCACCCGGATGCATACTTCATTGCA
AGACCTTCAGATCTTTATGTCTAAAGCAATCGAAGTTCTTCTTGGGATCCGCCACGAGAAAGAAAAATCTGATCAA
TCCCCATCATTTTTCGAGGCAGAGCAAATGAGATCAAAGTATGATGCTCGGCCAGTTCACAAGCCAATTGCTGCCC
GGGAAGGAAATTCGCACACAGTTATACTCTTCAATCCATCAGAACAGACGAGAGAGGAGGTGGTGACGGTTGTTGT
TAACCGCGCTGAAATCTCGGTTTTGGACTCAAACTGGACTTGTGTCCCTAGCCAAATTTCTCCTGAAGTGCAGCAT
GACGATACCAAACTATTCACCGGCAGACATCGCCTTTACTGGAAAGCTTCCATCCCAGCTCTTGGTCTGAGAACAT
ATTTCATTGCTAATGGGAATGTCGAGTGTGAGAAAGCTACTCCGTCTAAACTCAAATACGCTTCTGAGTTTGACCC
ATTTCCTTGTCCTCCTCCATATTCCTGCTCCAAACTGGACAACGACGTTACTGAGATCCGAAATGAACATCAGACT
CTTGTGTTTGATGTGAAGAACGGATCACTGCGGAAGATAGTCCATAGAAACGGATCAGAGACTGTTGTGGGAGAAG
AGATAGGTATGTACTCTAGTCCAGAGAGTGGAGCTTACCTGTTCAAACCAGATGGTGAAGCTCAGCCAATTGTTCA
ACCTGATGGACATGTAGTCACCTCTGAGGGTCTGCTGGTTCAAGAAGTCTTCTCTTACCCTAAAACCAAATGGGAG
AAATCACCCCTCTCTCAGAAAACTCGTCTTTACACTGGAGGTAATACGCTTCAGGATCAAGTGGTCGAGATAGAAT
ATCATGTTGAGCTTCTTGGTAATGATTTTGATGACCGGGAATTGATTGTCCGGTACAAGACTGATGTTGACAACAA
GAAGGTCTTCTATTCAGATCTCAATGGTTTCCAAATGAGCAGGAGAGAAACTTATGATAAGATCCCTCTTCAAGGA
AACTACTACCCAATGCCATCTCTCGCATTTATCCAAGGATCCAATGGTCAGAGATTCTCCGTGCACTCTCGTCAAT
CTCTCGGTGTTGCAAGCCTCAAAGAGGGTTGGTTGGAGATTATGCTGGACAGACGGTTGGTTCGTGATGACGGACG
GGGTCTAGGGCAAGGTGTGATGGATAACCGCGCAATGACCGTGGTATTTCACCTTCTTGCGGAATCTAACATTTCT
CAAGCAGACCCTGCTTCCAACACTAACCCGAGGAACCCTTCGCTTCTCTCTCACCTCATAGGTGCTCACTTAAACT
ACCCCATAAACACATTCATTGCCAAGAAACCGCAAGACATATCTGTGCGTGTTCCACAATACGGTTCCTTTGCTCC
TTTAGCCAAACCGTTACCATGTGACCTCCACATTGTAAATTTCAAGGTTCCTCGTCCATCCAAATACTCTCAGCAA
TTGGAAGAAGACAAGCCAAGGTTCGCTCTTATCCTCAATAGACGAGCTTGGGATTCAGCTTATTGCCATAAAGGAA
GACAAGTAAACTGCACAAGCATGGCTAATGAACCAGTAAACTTTTCCGACATGTTCAAAGATCTTGCAGCTTCAAA
GGTAAAACCAACTTCACTGAATCTCTTGCAAGAAGATATGGAGATTCTTGGGTACGATGACCAAGAGCTACCTCGA
GATAGTTCACAGCCACGGGAAGGACGTGTCTCGATCTCTCCCATGGAAATACGAGCTTATAAGCTTGAACTGCGAC
CTCACAAGTGAACCTGCTGAAGATC

FIG. 19 Cont.

GGCGCGCCTCGAGGCGATCGCAGATCTCATTATACCGTTAGAAGCATAGTTAAAATCTAAAGCTTGTCGTTAATTC
TAGTCATTTTACATTGTTGGGTTCTACATTATTAATGAATTTTCTAATGCAAATACAGAATTTAAATCAAAATTGT
TGAATTATGCTAAACATGTAACATACGTATATCTCCGCCTTGTGTGTTGTATTAACTTGAAGTTATCATAAGAACC
ACAAATACACTAGTAAATCTATGAGAAGGCAGGTGGCAACACAAACAAGAGTATCTAAGATTTTCATTTGTGACTA
TAGGAATATAATATCTCTTATCTGATTTAATGAATCCACATGTTCACTTCTCATTTGTCCACAAGATCACAACTTT
ATCTTCAATATTCACAACTTGTTATATCCACCACAATTTCATTCTTTTCACTTAGCCCCACAAAATACTTTGTCCC
CTTATTTGCCACCTTTTGTATTTAATTTATTCTTGTGGAGCTAAGTGTTCATATTATTCTTCTTCTCAAAAAAACA
AAAACAAAAAAAAAAGAGAAGAAAACCATGGCGAGGATCTCGTGTGACTTGAGATTTCTTCTCATCCCGGCAGCTTT
CATGTTCATCTACATCCAGATGAGGCTTTTCCAGACGCAATCACAGTATGCAGATCGCCTCAGTTCCGCTATCGAA
TCTGAGAACCATTGCACTAGTCAAATGCGAGGCCTCATAGATGAAGTTAGCATCAAACAGTCGCGGATTGTTGCCC
TCGAAGATATGAAGAACCGCCAGGACGAAGAACTTGTGCAGCTTAAGGATCTAATCCAGACGTTTGAAAAAAAAGG
AATAGCAAAACTCACTCAAGGTGGAGCCATGGCTCTAAGGTTGCATAGAAGGAACCATTTTTCGCCTAGAAATACG
GATCTGTTCCCGGATTTGGCAAAAGATCGTGTGGTTATCGTCTTGTATGTGCATAATCGGGCTCAGTATTTTCGAG
TCACAGTGGAAAGTTTGTCGAAGGTTAAAGGTATAAGTGAGACATTGTTGATTGTTAGTCATGATGGTTACTTTGA
AGAGATGAATAGGATTGTGGAGAGTATTAAGTTTTGTCAAGTGAAACAGATTTTCTCGCCTTATTCGCCTCATATA
TATCGTACTAGCTTCCCGGGTGTGACCCTGAATGATTGTAAGAACAAGGGTGATGAGGCAAAGGGGCATTGTGAAG
GTAATCCTGATCAGTATGGGAATCATCGGTCTCCGAAGATTGTATCTTTGAAGCATCACTGGTGGTGGATGATGAA
CACTGTATGGGATGGGTTGGAAGAGACTAAAGGACATGAGGGGCATATCCTTTTCATTGAAGAAGATCATTTTCTG
TTTCCTAATGCCTATCGTAACATACAGACTCTTACGAGGCTGAAACCCGCAAAGTGTCCTGACTGTTTTGCTGCTA
ATTTAGCACCGTCTGATGTGAAGTCAAGAGGAGAAGGGCTTGAAAGTTTGGTTGCAGAGAGAATGGGAAATGTTGG
GTATTCTTTTAATAGAAGTGTGTGGGAGAATATTCATCAGAAGGCAAGAGAGTTTTGTTTCTTTGATGATTACAAC
TGGGATATAACGATGTGGGCAACGGTTTTCCCGTCGTTTGGTTCCCCGGTGTACACATTGCGAGGGCCTAGGACTA
GTGCGGTACACTTTGGAAAATGTGGGTTGCATCAAGGTAGAGGAGATGAGGGTGATTGCATCGATAATGGGGTCGT
AAACATAGAAGTTAAGGAAACAGATAAAGTTGTGAACATAAAAGAAGGATGGGGAGTTCGGGTGTATAAGCATCA
GCGGGTTATAAAGCCGGTTTCGAAGGTTGGGGAGGTTGGGGCGATGATAGGGACCGACATTTATGTTTGGATTTTG
CCACTATGTATCGTTACAGCAGTAGCAGTGCATCTCCATGAAACGGATCCGCTAGAGTCCGCAAAAATCACCAGTC
TCTCTCTACAAATCTATCTCTCTCTATTTTTCTCCAGAATAATGTGTGAGTAGTTCCCAGATAAGGGAATTAGGGT
TCTTATAGGGTTTCGCTCATGTGTTGAGCATATAAGAAACCCTTAGTATGTATTTGTATTTGTAAAATACTTCTAT
CAATAAAATTTCTAATCCTAAAACCAAAATCCCGCGAGAGACCTCTTAATTAA

FIG. 20

CCATGGCGAGGATCTCGTGTGACTTGAGATTTCTTCTCATCCCGGCAGCTTTCATGTTCATCTACATCCAGATGAG
GCTTTTCCAGACGCAATCACAGTATGCAGATCGCCTCAGTTCCGCTATCGAATCTGAGAACCATTGCACTAGTCAA
ATGCGAGGCCTCATAGATGAAGTTAGCATCAAACAGTCGCGGATTGTTGCCCTCGAAGATATGAAGAACCGCCAGG
ACGAAGAACTTGTGCAGCTTAAGGATCTAATCCAGACGTTTGAAAAAAAAAGGAATAGCAAAACTCACTCAAGGTGG
AGCCATGGCTCTAAGGTTGCATAGAAGGAACCATTTTTCGCCTAGAAATACGGATCTGTTCCCGGATTTGGCAAAA
GATCGTGTGGTTATCGTCTTGTATGTGCATAATCGGGCTCAGTATTTTCGAGTCACAGTGGAAAGTTTGTCGAAGG
TTAAAGGTATAAGTGAGACATTGTTGATTGTTAGTCATGATGGTTACTTTGAAGAGATGAATAGGATTGTGGAGAG
TATTAAGTTTTGTCAAGTGAAACAGATTTTCTCGCCTTATTCGCCTCATATATATCGTACTAGCTTCCCGGGTGTG
ACCCTGAATGATTGTAAGAACAAGGGTGATGAGGCAAAGGGGCATTGTGAAGGTAATCCTGATCAGTATGGGAATC
ATCGGTCTCCGAAGATTGTATCTTTGAAGCATCACTGGTGGTGGATGATGAACACTGTATGGGATGGGTTGGAAGA
GACTAAAGGACATGAGGGGCATATCCTTTTCATTGAAGAAGATCATTTTCTGTTTCCTAATGCCTATCGTAACATA
CAGACTCTTACGAGGCTGAAACCCGCAAAGTGTCCTGACTGTTTTGCTGCTAATTTAGCACCGTCTGATGTGAAGT
CAAGAGGAGAAGGGCTTGAAAGTTTGGTTGCAGAGAGAATGGGAAATGTTGGGTATTCTTTTAATAGAAGTGTGTG
GGAGAATATTCATCAGAAGGCAAGAGAGTTTTGTTTCTTTGATGATTACAACTGGGATATAACGATGTGGGCAACG
GTTTTCCCGTCGTTTGGTTCCCCGGTGTACACATTGCGAGGGCCTAGGACTAGTGCGGTACACTTTGGAAAATGTG
GGTTGCATCAAGGTAGAGGAGATGAGGGTGATTGCATCGATAATGGGGTCGTAAACATAGAAGTTAAGGAAACAGA
TAAAGTTGTGAACATAAAAGAAGGATGGGGAGTTCGGGTGTATAAGCATCAAGCGGGTTATAAAGCCGGTTTCGAA
GGTTGGGGAGGTTGGGGCGATGATAGGGACCGACATTTATGTTTGGATTTTGCCACTATGTATCGTTACAGCAGTA
GCAGTGCATCTCCATGAAACGGATCC

FIG. 21

CCATGGCGAGGATCTCGTGTGACTTGAGATTTCTTCTCATCCCGGCAGCTTTCATGTTCATCTACATCCAGATGAG
GCTTTTCCAGACGCAATCACAGTATGCAGATCGCCTCAGTTCCGCTATCGAATCTGAGAACCATTGCACTAGTCAA
ATGCGAGGCCTCATAGATGAAGTTAGCATCAAACAGTCGCGGATTGTTGCCCTCGAAGATATGAAGAACCGCCAGG
ACGAAGAACTTGTGCAGCTTAAGGATCTAATCCAGACGTTTGAAAAAAAAGGAATAGCAAAACTCACTCAAGGTGG
AGCCATGG

FIG. 22A

CCATGGCGAGAGGGAGCAGATCAGTGGGTAGCAGCAGCAGCAAATGGAGGTACTGCAACCCTTCCTATTACTTGAA
GCGCCCAAAGCGTCTTGCTCTGCTCTTCATCGTTTTCGTTTGTGTCTCTTTCGTTTTCTGGGACCGTCAAACTCTC
GTCAGAGAGCACCAGGTTGAAATTTCTGAGCTGCAGAAAGAAGTGACTGATTTGAAAAATTTGGTGGATGATTTAA
ATAACAAACAAGGTGGTACCTCTGGGAAAACTGACTTGGGGACCATGG

FIG. 22B

GGCGCGCCTCGAGGCGATCGCAGATCCGATATAACAAAATTTGAATCGCACAGATCGATCTCTTTGGAGATTCTAT
ACCTAGAAAATGGAGACGATTTTCAAATCTCTGTAAAAATTCTGGTTTCTTCTTGACGGAAGAAGACGACGACTCC
AATATTTCGGTTAGTACTGAACCGGAAAGTTTGACTGGTGCAACCAATTTAATGTACCGTACGTAACGCACCAATC
GGATTTTGTATTCAATGGGCCTTATCTGTGAGCCCATTAATTGATGTGACGGCCTAAACTAAATCCGAACGGTTTA
TTTCAGCGATCCGCGACGGTTTGTATTCAGCCAATAGCAATCAATTATGTAGCAGTGGTGATCCTCGTCAAACCAG
TAAAGCTAGATCTGGACCGTTGAATTGGTGCAAGAAAGCACATGTTGTGATATTTTTACCCGTACGATTAGAAAAC
TTGAGAAACACATTGATAATCGATAAAAACCGTCCGATCATATAAATCCGCTTTACCATCGTTGCCTATAAATTAA
TATCAATAGCCGTACACGCGTGAAGACTGACAATATTATCTTTTTCGAATTCGGAGCTCAAGTTTGAAATTCGGAG
AAGCTAGAGAGTTTTCTGATAACCATGGCGAGAGGGAGCAGATCAGTGGGTAGCAGCAGCAGCAAATGGAGGTACT
GCAACCCTTCCTATTACTTGAAGCGCCCAAAGCGTCTTGCTCTGCTCTTCATCGTTTTCGTTTGTGTCTCTTTCGT
TTTCTGGGACCGTCAAACTCTCGTCAGAGAGCACCAGGTTGAAATTTCTGAGCTGCAGAAAGAAGTGACTGATTTG
AAAAATTTGGTGGATGATTTAAATAACAAACAAGGTGGTACCTCTGGGAAAACTGACTTGGGGACCATGGGACAGA
TGCCTGTGGCTGCTGTAGTGGTTATGGCCTGCAGTCGTGCAGACTATCTTGAAAGGACTGTTAAATCAGTTTTAAC
ATATCAAACTCCCGTTGCTTCAAAATATCCTCTATTTATATCTCAGGATGGATCTGATCAAGCTGTCAAGAGCAAG
TCATTGAGCTATAATCAATTAACATATATGCAGCACTTGGATTTTGAACCAGTGGTCACTGAAAGGCCTGGCGAAC
TGACTGCGTACTACAAGATTGCACGTCACTACAAGTGGGCACTGGACCAGTTGTTTTACAAACACAAATTTAGTCG
AGTGATTATACTAGAAGATGATATGGAAATTGCTCCAGACTTCTTTGATTACTTTGAGGCTGCAGCTAGTCTCATG
GATAGGGATAAAACCATTATGGCTGCTTCATCATGGAATGATAATGGACAGAAGCAGTTTGTGCATGATCCCTATG
CGCTATACCGATCAGATTTTTTTCCTGGCCTTGGGTGGATGCTCAAGAGATCGACTTGGGATGAGTTATCACCAAA
GTGGCCAAAGGCTTACTGGGATGATTGGCTGAGACTAAAGGAAAACCATAAAGGCCGCCAATTCATTCGACCGGAA
GTCTGTAGAACATACAATTTTGGTGAACATGGGTCTAGTTTGGGACAGTTTTTCAGTCAGTATCTGGAACCTATAA
AGCTAAACGATGTGACGGTTGACTGGAAAGCAAAGGACCTGGGATACCTGACAGAGGGAAACTATACCAAGTACTT
TTCTGGCTTAGTGAGACAAGCACGACCAATTCAAGGTTCTGACCTTGTCTTAAAGGCTCAAAACATAAAGGATGAT
GTTCGTATCCGGTATAAAGACCAAGTAGAGTTTGAACGCATTGCAGGGGAATTTGGTATATTTGAAGAATGGAAGG
ATGGTGTGCCTCGAACAGCATATAAAGGAGTAGTGGTGTTTCGAATCCAGACAACAAGACGTGTATTCCTGGTTGG
GCCAGATTCTGTAATGCAGCTTGGAATTCGAAATTCCTGATGCGGATCCGCTAGAGTCCGCAAAAATCACCAGTCT
CTCTCTACAAATCTATCTCTCTCTATTTTTCTCCAGAATAATGTGTGAGTAGTTCCCAGATAAGGGAATTAGGGTT

FIG. 23

CTTATAGGGTTTCGCTCATGTGTTGAGCATATAAGAAACCCTTAGTATGTATTTGTATTTGTAAAATACTTCTATC
AATAAAATTTCTAATCCTAAAACCAAAATCCCGCGCCTCGAGGCGATCGCAGATCTAATCTAACCAATTACGATAC
GCTTTGGGTACACTTGATTTTTGTTTCAGTGGTTACATATATCTTGTTTTATATGCTATCTTTAAGGATCTGCACA
AAGATTATTTGTTGATGTTCTTGATGGGGCTCAGAAGATTTGATATGATACACTCTAATCTTTAGGAGATACCAGC
CAGGATTATATTCAGTAAGACAATCAAATTTTACGTGTTCAAACTCGTTATCTTTTCATTCAAAGGATGAGCCAGA
ATCTTTATAGAATGATTGCAATCGAGAATATGTTCGGCCGATATGCCTTTGTTGGCTTCAATATTCTACATATCAC
ACAAGAATCGACCGTATTGTACCCTCTTTCCATAAAGGAAAACACAATATGCAGATGCTTTTTTCCCACATGCAGT
AACATATAGGTATTCAAAAATGGCTAAAAGAAGTTGGATAACAAATTGACAACTATTTCCATTTCTGTTATATAAA
TTTCACAACACACAAAAGCCCGTAATCAAGAGTCTGCCCATGTACGAAATAACTTCTATTATTTGGTATTGGGCCT
AAGCCCAGCTCAGAGTACGTGGGGGTACCACATATAGGAAGGTAACAAAATACTGCAAGATAGCCCCATAACGTAC
CAGCCTCTCCTTACCACGAAGAGATAAGATATAAGACCCACCCTGCCACGTGTCACATCGTCATGGTGGTTAATGA
TAAGGGATTACATCCTTCTATGTTTGTGGACATGATGCATGTAATGTCATGAGCCACAGGATCCAATGGCCACAGG
AACGTAAGAATGTAGATAGATTTGATTTTGTCCGTTAGATAGCAAACAACATTATAAAAGGTGTGTATCAATAGGA
ACTAATTCACTCATTGGATTCATAGAAGTCCATTCCTCCTAAGTATCTAGAAACCATGGCGAGAGGGAGCAGATCA
GTGGGTAGCAGCAGCAGCAAATGGAGGTACTGCAACCCTTCCTATTACTTGAAGCGCCCAAAGCGTCTTGCTCTGC
TCTTCATCGTTTTCGTTTGTGTCTCTTTCGTTTTCTGGGACCGTCAAACTCTCGTCAGAGAGCACCAGGTTGAAAT
TTCTGAGCTGCAGAAAGAAGTGACTGATTTGAAAAATTTGGTGGATGATTTAAATAACAAACAAGGTGGTACCTCT
GGGAAAACTGACTTGGGGACCATGGATTCCAATTCAGGCGCCGTCGTTGATATCACAACTAAAGATCTATACGATA
GGATTGAGTTTCTTGATACAGATGGTGGTCCATGGAAACAAGGTTGGAGAGTTACGTATAAAGACGATGAGTGGGA
GAAAGAGAAGCTCAAAATCTTCGTTGTTCCTCATTCTCATAACGATCCTGGTTGGAAATTGACTGTAGAGGAGTAT
TATCAGAGACAATCCAGACATATTCTTGACACCATTGTTGAGACTTTATCTAAGGTATGACGAAAGTTTTTGCTTT
TGGTTTTAATATTTTAATTCTCTCCCATGGTTATCCCGTGAACAATCTTAAATGTCTTAAAATTCTCATGACGTCA
TTAAACTCTATAACCAAACTTCTTTGCTGGGTTCTGTTTTTTTTTAGTTTCGTGATGAAACAGAGTTCTAGAAGTT
CGTTCTTTTGGAAAATTTGAAGTCTTTGGAGCTAAAGTTTGTTTTTTTATTACTGGGTTTTGAGATTGAAGGATAG
CTAGAATCTTATTTGTGTGGGGGTTTGTTTTGAATATGTTTAATAGGATTCAAGAAGAAAGTTTATATGGGAGGAG
ATGTCATATCTGGAGAGATGGTGGAGAGACGCTTCACCTAATAAACAAGAAGCTTTGACTAAATTGGTTAAGGATG
GGCAGCTAGAGATTGTTGGAGGTGGCTGGGTTATGAATGATGAGGCTAATTCACATTATTTTGCCATAATTGAACA

FIG. 23 Cont.

GATAGCAGAGGGTAATATGTGGCTGAATGACACAATTGGGGTTATTCCTAAGAATTCTTGGGCTATAGATCCCTTT
GGCTATTCATCAACCATGGCTTATCTTCTCCGGCGTATGGGTTTTGAAAACATGCTTATTCAAAGGACTCATTACG
AGCTCAAGAAAGACCTTGCCCAGCATAAGAATCTTGAATATATTTGGCGTCAGAGCTGGGATGCTATGGAAACCAC
AGATATCTTTGTTCATATGATGCCGTTTTATTCATACGATATCCCACACACTTGTGGACCAGAGCCTGCAATTTGC
TGTCAGTTTGATTTCGCTCGGATGCGGGGATTTAAGTATGAACTTTGTCCATGGGGAAAGCACCCAGTGGAGACCA
CACTAGAAAATGTGCAGGAGAGGGCATTAAAGCTTCTGGATCAATACAGGAAAAAATCCACTCTATATCGAACTAA
TACACTTCTTATACCTCTTGGAGATGATTTTAGGTACATTAGTATCGATGAAGCCGAGGCTCAGTTCCGTAACTAC
CAGATGTTGTTTGATCACATCAACTCTAATCCTAGTCTAAACGCAGAAGCAAAGTTTGGTACTTTGGAGGATTATT
TCAGAACAGTCCGAGAAGAAGCAGACAGAGTGAATTATTCTCGTCCTGGTGAGGTTGGCTCTGGTCAGGTTGTTGG
TTTCCCTTCTCTGTCAGGTGACTTCTTTACATATGCAGATAGGCAACAAGACTATTGGAGTGGTTATTATGTTTCA
AGACCTTTCTTCAAAGCTGTTGATCGTGTGCTCGAGCATACCCTTCGTGGAGCTGAGATCATGATGTCATTTCTGC
TAGGTTATTGCCATCGAATTCAATGTGAGAAATTTCCAACAAGTTTTACGTATAAGTTGACTGCTGCAAGAAGAAA
TCTGGCTCTTTTCCAGCACCATGATGGGGTAACTGGAACTGCTAAGGATTATGTGGTACAAGATTACGGCACCCGG
ATGCATACTTCATTGCAAGACCTTCAGATCTTTATGTCTAAAGCAATCGAAGTTCTTCTTGGGATCCGCCACGAGA
AAGAAAAATCTGATCAATCCCCATCATTTTTCGAGGCAGAGCAAATGAGATCAAAGTATGATGCTCGGCCAGTTCA
CAAGCCAATTGCTGCCCGGGAAGGAAATTCGCACACAGTTATACTCTTCAATCCATCAGAACAGACGAGAGAGGAG
GTGGTGACGGTTGTTGTTAACCGCGCTGAAATCTCGGTTTTGGACTCAAACTGGACTTGTGTCCCTAGCCAAATTT
CTCCTGAAGTGCAGCATGACGATACCAAACTATTCACCGGCAGACATCGCCTTTACTGGAAAGCTTCCATCCCAGC
TCTTGGTCTGAGAACATATTTCATTGCTAATGGGAATGTCGAGTGTGAGAAAGCTACTCCGTCTAAACTCAAATAC
GCTTCTGAGTTTGACCCATTTCCTTGTCCTCCTCCATATTCCTGCTCCAAACTGGACAACGACGTTACTGAGATCC
GAAATGAACATCAGACTCTTGTGTTTGATGTGAAGAACGGATCACTGCGGAAGATAGTCCATAGAAACGGATCAGA
GACTGTTGTGGGAGAAGAGATAGGTATGTACTCTAGTCCAGAGAGTGGAGCTTACCTGTTCAAACCAGATGGTGAA
GCTCAGCCAATTGTTCAACCTGATGGACATGTAGTCACCTCTGAGGGTCTGCTGGTTCAAGAAGTCTTCTCTTACC
CTAAAACCAAATGGGAGAAATCACCCCTCTCTCAGAAAACTCGTCTTTACACTGGAGGTAATACGCTTCAGGATCA
AGTGGTCGAGATAGAATATCATGTTGAGCTTCTTGGTAATGATTTTGATGACCGGGAATTGATTGTCCGGTACAAG
ACTGATGTTGACAACAAGAAGGTCTTCTATTCAGATCTCAATGGTTTCCAAATGAGCAGGAGAGAAACTTATGATA
AGATCCCTCTTCAAGGAAACTACTACCCAATGCCATCTCTCGCATTTATCCAAGGATCCAATGGTCAGAGATTCTC

FIG. 23 Cont.

CGTGCACTCTCGTCAATCTCTCGGTGTTGCAAGCCTCAAAGAGGGTTGGTTGGAGATTATGCTGGACAGACGGTTG
GTTCGTGATGACGGACGGGGTCTAGGGCAAGGTGTGATGGATAACCGCGCAATGACCGTGGTATTTCACCTTCTTG
CGGAATCTAACATTTCTCAAGCAGACCCTGCTTCCAACACTAACCCGAGGAACCCTTCGCTTCTCTCTCACCTCAT
AGGTGCTCACTTAAACTACCCCATAAACACATTCATTGCCAAGAAACCGCAAGACATATCTGTGCGTGTTCCACAA
TACGGTTCCTTTGCTCCTTTAGCCAAACCGTTACCATGTGACCTCCACATTGTAAATTTCAAGGTTCCTCGTCCAT
CCAAATACTCTCAGCAATTGGAAGAAGACAAGCCAAGGTTCGCTCTTATCCTCAATAGACGAGCTTGGGATTCAGC
TTATTGCCATAAAGGAAGACAAGTAAACTGCACAAGCATGGCTAATGAACCAGTAAACTTTTCCGACATGTTCAAA
GATCTTGCAGCTTCAAAGGTAAAACCAACTTCACTGAATCTCTTGCAAGAAGATATGGAGATTCTTGGGTACGATG
ACCAAGAGCTACCTCGAGATAGTTCACAGCCACGGGAAGGACGTGTCTCGATCTCTCCCATGGAAATACGAGCTTA
TAAGCTTGAACTGCGACCTCACAAGTGAACCTGCTGAAGATCCGCTAGAGTCCGCAAAAATCACCAGTCTCTCTCT
ACAAATCTATCTCTCTCTATTTTTCTCCAGAATAATGTGTGAGTAGTTCCCAGATAAGGGAATTAGGGTTCTTATA
GGGTTTCGCTCATGTGTTGAGCATATAAGAAACCCTTAGTATGTATTTGTATTTGTAAAATACTTCTATCAATAAA
ATTTCTAATCCTAAAACCAAAATCCCGCGCGCGCCTCGAGGCGATCGCAGATCTCATTATACCGTTAGAAGCATAG
TTAAAATCTAAAGCTTGTCGTTAATTCTAGTCATTTTACATTGTTGGGTTCTACATTATTAATGAATTTTCTAATG
CAAATACAGAATTTAAATCAAAATTGTTGAATTATGCTAAACATGTAACATACGTATATCTCCGCCTTGTGTGTTG
TATTAACTTGAAGTTATCATAAGAACCACAAATACACTAGTAAATCTATGAGAAGGCAGGTGGCAACACAAACAAG
AGTATCTAAGATTTTCATTTGTGACTATAGGAATATAATATCTCTTATCTGATTTAATGAATCCACATGTTCACTT
CTCATTTGTCCACAAGATCACAACTTTATCTTCAATATTCACAACTTGTTATATCCACCACAATTTCATTCTTTTC
ACTTAGCCCCACAAAATACTTTGTCCCCTTATTTGCCACCTTTTGTATTTAATTTATTCTTGTGGAGCTAAGTGTT
CATATTATTCTTCTTCTCAAAAAAACAAAAACAAAAAAAAAAGAGAAGAAAACCATGGCGAGAGGGAGCAGATCAGT
GGGTAGCAGCAGCAGCAAATGGAGGTACTGCAACCCTTCCTATTACTTGAAGCGCCCAAAGCGTCTTGCTCTGCTC
TTCATCGTTTTCGTTTGTGTCTCTTTCGTTTTCTGGGACCGTCAAACTCTCGTCAGAGAGCACCAGGTTGAAATTT
CTGAGCTGCAGAAAGAAGTGACTGATTTGAAAAATTTGGTGGATGATTTAAATAACAAACAAGGTGGTACCTCTGG
GAAAACTGACTTGGGGACCATGGCTCTAAGGTTGCATAGAAGGAACCATTTTTCGCCTAGAAATACGGATCTGTTC
CCGGATTTGGCAAAAGATCGTGTGGTTATCGTCTTGTATGTGCATAATCGGGCTCAGTATTTTCGAGTCACAGTGG
AAAGTTTGTCGAAGGTTAAAGGTATAAGTGAGACATTGTTGATTGTTAGTCATGATGGTTACTTTGAAGAGATGAA
TAGGATTGTGGAGAGTATTAAGTTTTGTCAAGTGAAACAGATTTTCTCGCCTTATTCGCCTCATATATATCGTACT

FIG. 23 Cont.

AGCTTCCCGGGTGTGACCCTGAATGATTGTAAGAACAAGGGTGATGAGGCAAAGGGGCATTGTGAAGGTAATCCTG
ATCAGTATGGGAATCATCGGTCTCCGAAGATTGTATCTTTGAAGCATCACTGGTGGTGGATGATGAACACTGTATG
GGATGGGTTGGAAGAGACTAAAGGACATGAGGGGCATATCCTTTTCATTGAAGAAGATCATTTTCTGTTTCCTAAT
GCCTATCGTAACATACAGACTCTTACGAGGCTGAAACCCGCAAAGTGTCCTGACTGTTTTGCTGCTAATTTAGCAC
CGTCTGATGTGAAGTCAAGAGGAGAAGGGCTTGAAAGTTTGGTTGCAGAGAGAATGGGAAATGTTGGGTATTCTTT
TAATAGAAGTGTGTGGGAGAATATTCATCAGAAGGCAAGAGAGTTTTGTTTCTTTGATGATTACAACTGGGATATA
ACGATGTGGGCAACGGTTTTCCCGTCGTTTGGTTCCCCGGTGTACACATTGCGAGGGCCTAGGACTAGTGCGGTAC
ACTTTGGAAAATGTGGGTTGCATCAAGGTAGAGGAGATGAGGGTGATTGCATCGATAATGGGGTCGTAAACATAGA
AGTTAAGGAAACAGATAAAGTTGTGAACATAAAAGAAGGATGGGGAGTTCGGGTGTATAAGCATCAAGCGGGTTAT
AAAGCCGGTTTCGAAGGTTGGGGAGGTTGGGGCGATGATAGGGACCGACATTTATGTTTGGATTTTGCCACTATGT
ATCGTTACAGCAGTAGCAGTGCATCTCCATGAAACGGATCCGCTAGAGTCCGCAAAAATCACCAGTCTCTCTCTAC
AAATCTATCTCTCTCTATTTTTCTCCAGAATAATGTGTGAGTAGTTCCCAGATAAGGGAATTAGGGTTCTTATAGG
GTTTCGCTCATGTGTTGAGCATATAAGAAACCCTTAGTATGTATTTGTATTTGTAAAATACTTCTATCAATAAAAT
TTCTAATCCTAAAACCAAAATCCCGCGAGAGACCTCTTAATTAA

FIG. 23 Cont.

GGCGCGCCTCGAGGCGATCGCAGATCCGATATAACAAAATTTGAATCGCACAGATCGATCTCTTTGGAGATTCTAT
ACCTAGAAAATGGAGACGATTTTCAAATCTCTGTAAAAATTCTGGTTTCTTCTTGACGGAAGAAGACGACGACTCC
AATATTTCGGTTAGTACTGAACCGGAAAGTTTGACTGGTGCAACCAATTTAATGTACCGTACGTAACGCACCAATC
GGATTTTGTATTCAATGGGCCTTATCTGTGAGCCCATTAATTGATGTGACGGCCTAAACTAAATCCGAACGGTTTA
TTTCAGCGATCCGCGACGGTTTGTATTCAGCCAATAGCAATCAATTATGTAGCAGTGGTGATCCTCGTCAAACCAG
TAAAGCTAGATCTGGACCGTTGAATTGGTGCAAGAAAGCACATGTTGTGATATTTTTACCCGTACGATTAGAAAAC
TTGAGAAACACATTGATAATCGATAAAAACCGTCCGATCATATAAATCCGCTTTACCATCGTTGCCTATAAATTAA
TATCAATAGCCGTACACGCGTGAAGACTGACAATATTATCTTTTTCGAATTCGGAGCTCAAGTTTGAAATTCGGAG
AAGCTAGAGAGTTTTCTGATAACCATGGCGAGAGGGAGCAGATCAGTGGGTAGCAGCAGCAGCAAATGGAGGTACT
GCAACCCTTCCTATTACTTGAAGCGCCCAAAGCGTCTTGCTCTGCTCTTCATCGTTTTCGTTTGTGTCTCTTTCGT
TTTCTGGGACCGTCAAACTCTCGTCAGAGAGCACCAGGTTGAAATTTCTGAGCTGCAGAAAGAAGTGACTGATTTG
AAAAATTTGGTGGATGATTTAAATAACAAACAAGGTGGTACCTCTGGGAAAACTGACTTGGGGACCATGGGACAGA
TGCCTGTGGCTGCTGTAGTGGTTATGGCCTGCAGTCGTGCAGACTATCTTGAAAGGACTGTTAAATCAGTTTTAAC
ATATCAAACTCCCGTTGCTTCAAAATATCCTCTATTTATATCTCAGGATGGATCTGATCAAGCTGTCAAGAGCAAG
TCATTGAGCTATAATCAATTAACATATATGCAGCACTTGGATTTTGAACCAGTGGTCACTGAAAGGCCTGGCGAAC
TGACTGCGTACTACAAGATTGCACGTCACTACAAGTGGGCACTGGACCAGTTGTTTTACAAACACAAATTTAGTCG
AGTGATTATACTAGAAGATGATATGGAAATTGCTCCAGACTTCTTTGATTACTTTGAGGCTGCAGCTAGTCTCATG
GATAGGGATAAAACCATTATGGCTGCTTCATCATGGAATGATAATGGACAGAAGCAGTTTGTGCATGATCCCTATG
CGCTATACCGATCAGATTTTTTTCCTGGCCTTGGGTGGATGCTCAAGAGATCGACTTGGGATGAGTTATCACCAAA
GTGGCCAAAGGCTTACTGGGATGATTGGCTGAGACTAAAGGAAAACCATAAAGGCCGCCAATTCATTCGACCGGAA
GTCTGTAGAACATACAATTTTGGTGAACATGGGTCTAGTTTGGGACAGTTTTTCAGTCAGTATCTGGAACCTATAA
AGCTAAACGATGTGACGGTTGACTGGAAAGCAAAGGACCTGGGATACCTGACAGAGGGAAACTATACCAAGTACTT
TTCTGGCTTAGTGAGACAAGCACGACCAATTCAAGGTTCTGACCTTGTCTTAAAGGCTCAAAACATAAAGGATGAT
GTTCGTATCCGGTATAAAGACCAAGTAGAGTTTGAACGCATTGCAGGGGAATTTGGTATATTTGAAGAATGGAAGG
ATGGTGTGCCTCGAACAGCATATAAAGGAGTAGTGGTGTTTCGAATCCAGACAACAAGACGTGTATTCCTGGTTGG
GCCAGATTCTGTAATGCAGCTTGGAATTCGAAATTCCTGATGCGGATCCGCTAGAGTCCGCAAAAATCACCAGTCT
CTCTCTACAAATCTATCTCTCTCTATTTTTCTCCAGAATAATGTGTGAGTAGTTCCCAGATAAGGGAATTAGGGTT
CTTATAGGGTTTCGCTCATGTGTTGAGCATATAAGAAACCCTTAGTATGTATTTGTATTTGTAAAATACTTCTATC

FIG. 24

GGATCCGATATAACAAAATTTGAATCGCACAGATCGATCTCTTTGGAGATTCTATACCTAGAAAATGGAGACGATT
TTCAAATCTCTGTAAAAATTCTGGTTTCTTCTTGACGGAAGAAGACGACGACTCCAATATTTCGGTTAGTACTGAA
CCGGAAAGTTTGACTGGTGCAACCAATTTAATGTACCGTACGTAACGCACCAATCGGATTTTGTATTCAATGGGCC
TTATCTGTGAGCCCATTAATTGATGTGACGGCCTAAACTAAATCCGAACGGTTTATTTCAGCGATCCGCGACGGTT
TGTATTCAGCCAATAGCAATCAATTATGTAGCAGTGGTGATCCTCGTCAAACCAGTAAAGCTAGATCTGGACCGTT
GAATTGGTGCAAGAAAGCACATGTTGTGATATTTTTACCCGTACGATTAGAAAACTTGAGAAACACATTGATAATC
GATAAAAAACCGTCCGATCATATAAATCCGCTTTACCATCGTTGCCTATAAATTAATATCAATAGCCGTACACGCGT
GAAGACTGACAATATTATCTTTTTCGAATTCGGAGCTCAAGTTTGAAATTCGGAGAAGCTAGAGAGTTTTCTGATA
ACCATGG

FIG. 25

CCATGGCGAGAGGGAGCAGATCAGTGGGTAGCAGCAGCAGCAAATGGAGGTACTGCAACCCTTCCTATTACTTGAA
GCGCCCAAAGCGTCTTGCTCTGCTCTTCATCGTTTTCGTTTGTGTCTCTTTCGTTTTCTGGGACCGTCAAACTCTC
GTCAGAGAGCACCAGGTTGAAATTTCTGAGCTGCAGAAAGAAGTGACTGATTTGAAAAATTTGGTGGATGATTTAA
ATAACAAACAAGGTGGTACCTCTGGGAAAACTGACTTGGGGACCATGGGACAGATGCCTGTGGCTGCTGTAGTGGT
TATGGCCTGCAGTCGTGCAGACTATCTTGAAAGGACTGTTAAATCAGTTTTAACATATCAAACTCCCGTTGCTTCA
AAATATCCTCTATTTATATCTCAGGATGGATCTGATCAAGCTGTCAAGAGCAAGTCATTGAGCTATAATCAATTAA
CATATATGCAGCACTTGGATTTTGAACCAGTGGTCACTGAAAGGCCTGGCGAACTGACTGCGTACTACAAGATTGC
ACGTCACTACAAGTGGGCACTGGACCAGTTGTTTTACAAACACAAATTTAGTCGAGTGATTATACTAGAAGATGAT
ATGGAAATTGCTCCAGACTTCTTTGATTACTTTGAGGCTGCAGCTAGTCTCATGGATAGGGATAAAACCATTATGG
CTGCTTCATCATGGAATGATAATGGACAGAAGCAGTTTGTGCATGATCCCTATGCGCTATACCGATCAGATTTTTT
TCCTGGCCTTGGGTGGATGCTCAAGAGATCGACTTGGGATGAGTTATCACCAAAGTGGCCAAAGGCTTACTGGGAT
GATTGGCTGAGACTAAAGGAAAACCATAAAGGCCGCCAATTCATTCGACCGGAAGTCTGTAGAACATACAATTTTG
GTGAACATGGGTCTAGTTTGGGACAGTTTTTCAGTCAGTATCTGGAACCTATAAAGCTAAACGATGTGACGGTTGA
CTGGAAAGCAAAGGACCTGGGATACCTGACAGAGGGAAACTATACCAAGTACTTTTCTGGCTTAGTGAGACAAGCA
CGACCAATTCAAGGTTCTGACCTTGTCTTAAAGGCTCAAAACATAAAGGATGATGTTCGTATCCGGTATAAAGACC
AAGTAGAGTTTGAACGCATTGCAGGGGAATTTGGTATATTTGAAGAATGGAAGGATGGTGTGCCTCGAACAGCATA
TAAAGGAGTAGTGGTGTTTCGAATCCAGACAACAAGACGTGTATTCCTGGTTGGGCCAGATTCTGTAATGCAGCTT
GGAATTCGAAATTCCTGATGCGGATCC

FIG. 26

GGCGCGCCTCGAGGCGATCGCAGATCTAATCTAACCAATTACGATACGCTTTGGGTACACTTGATTTTTGTTTCAG
TGGTTACATATATCTTGTTTTATATGCTATCTTTAAGGATCTGCACAAAGATTATTTGTTGATGTTCTTGATGGGG
CTCAGAAGATTTGATATGATACACTCTAATCTTTAGGAGATACCAGCCAGGATTATATTCAGTAAGACAATCAAAT
TTTACGTGTTCAAACTCGTTATCTTTTCATTCAAAGGATGAGCCAGAATCTTTATAGAATGATTGCAATCGAGAAT
ATGTTCGGCCGATATGCCTTTGTTGGCTTCAATATTCTACATATCACACAAGAATCGACCGTATTGTACCCTCTTT
CCATAAAGGAAAACACAATATGCAGATGCTTTTTTCCCACATGCAGTAACATATAGGTATTCAAAAATGGCTAAAA
GAAGTTGGATAACAAATTGACAACTATTTCCATTTCTGTTATATAAATTTCACAACACACAAAAGCCCGTAATCAA
GAGTCTGCCCATGTACGAAATAACTTCTATTATTTGGTATTGGGCCTAAGCCCAGCTCAGAGTACGTGGGGGTACC
ACATATAGGAAGGTAACAAAATACTGCAAGATAGCCCCATAACGTACCAGCCTCTCCTTACCACGAAGAGATAAGA
TATAAGACCCACCCTGCCACGTGTCACATCGTCATGGTGGTTAATGATAAGGGATTACATCCTTCTATGTTTGTGG
ACATGATGCATGTAATGTCATGAGCCACAGGATCCAATGGCCACAGGAACGTAAGAATGTAGATAGATTTGATTTT
GTCCGTTAGATAGCAAACAACATTATAAAAGGTGTGTATCAATAGGAACTAATTCACTCATTGGATTCATAGAAGT
CCATTCCTCCTAAGTATCTAGAAACCATGGCGAGAGGGAGCAGATCAGTGGGTAGCAGCAGCAGCAAATGGAGGTA
CTGCAACCCTTCCTATTACTTGAAGCGCCCAAAGCGTCTTGCTCTGCTCTTCATCGTTTTCGTTTGTGTCTCTTTC
GTTTTCTGGGACCGTCAAACTCTCGTCAGAGAGCACCAGGTTGAAATTTCTGAGCTGCAGAAAGAAGTGACTGATT
TGAAAAATTTGGTGGATGATTTAAATAACAAACAAGGTGGTACCTCTGGGAAAACTGACTTGGGGACCATGGATTC
CAATTCAGGCGCCGTCGTTGATATCACAACTAAAGATCTATACGATAGGATTGAGTTTCTTGATACAGATGGTGGT
CCATGGAAACAAGGTTGGAGAGTTACGTATAAAGACGATGAGTGGGAGAAAGAGAAGCTCAAAATCTTCGTTGTTC
CTCATTCTCATAACGATCCTGGTTGGAAATTGACTGTAGAGGAGTATTATCAGAGACAATCCAGACATATTCTTGA
CACCATTGTTGAGACTTTATCTAAGGTATGACGAAAGTTTTTGCTTTTGGTTTTAATATTTTAATTCTCTCCCATG
GTTATCCCGTGAACAATCTTAAATGTCTTAAAATTCTCATGACGTCATTAAACTCTATAACCAAACTTCTTTGCTG
GGTTCTGTTTTTTTTTAGTTTCGTGATGAAACAGAGTTCTAGAAGTTCGTTCTTTTGGAAAATTTGAAGTCTTTGG
AGCTAAAGTTTGTTTTTTTATTACTGGGTTTTGAGATTGAAGGATAGCTAGAATCTTATTTGTGTGGGGGTTTGTT
TTGAATATGTTTAATAGGATTCAAGAAGAAAGTTTATATGGGAGGAGATGTCATATCTGGAGAGATGGTGGAGAGA
CGCTTCACCTAATAAACAAGAAGCTTTGACTAAATTGGTTAAGGATGGGCAGCTAGAGATTGTTGGAGGTGGCTGG

FIG. 27

GTTATGAATGATGAGGCTAATTCACATTATTTTGCCATAATTGAACAGATAGCAGAGGGTAATATGTGGCTGAATG
ACACAATTGGGGTTATTCCTAAGAATTCTTGGGCTATAGATCCCTTTGGCTATTCATCAACCATGGCTTATCTTCT
CCGGCGTATGGGTTTTGAAAACATGCTTATTCAAAGGACTCATTACGAGCTCAAGAAAGACCTTGCCCAGCATAAG
AATCTTGAATATATTTGGCGTCAGAGCTGGGATGCTATGGAAACCACAGATATCTTTGTTCATATGATGCCGTTTT
ATTCATACGATATCCCACACACTTGTGGACCAGAGCCTGCAATTTGCTGTCAGTTTGATTTCGCTCGGATGCGGGG
ATTTAAGTATGAACTTTGTCCATGGGGAAAGCACCCAGTGGAGACCACACTAGAAAATGTGCAGGAGAGGGCATTA
AAGCTTCTGGATCAATACAGGAAAAAATCCACTCTATATCGAACTAATACACTTCTTATACCTCTTGGAGATGATT
TTAGGTACATTAGTATCGATGAAGCCGAGGCTCAGTTCCGTAACTACCAGATGTTGTTTGATCACATCAACTCTAA
TCCTAGTCTAAACGCAGAAGCAAAGTTTGGTACTTTGGAGGATTATTTCAGAACAGTCCGAGAAGAAGCAGACAGA
GTGAATTATTCTCGTCCTGGTGAGGTTGGCTCTGGTCAGGTTGTTGGTTTCCCTTCTCTGTCAGGTGACTTCTTTA
CATATGCAGATAGGCAACAAGACTATTGGAGTGGTTATTATGTTTCAAGACCTTTCTTCAAAGCTGTTGATCGTGT
GCTCGAGCATACCCTTCGTGGAGCTGAGATCATGATGTCATTTCTGCTAGGTTATTGCCATCGAATTCAATGTGAG
AAATTTCCAACAAGTTTTACGTATAAGTTGACTGCTGCAAGAAGAAATCTGGCTCTTTTCCAGCACCATGATGGGG
TAACTGGAACTGCTAAGGATTATGTGGTACAAGATTACGGCACCCGGATGCATACTTCATTGCAAGACCTTCAGAT
CTTTATGTCTAAAGCAATCGAAGTTCTTCTTGGGATCCGCCACGAGAAAGAAAAATCTGATCAATCCCCATCATTT
TTCGAGGCAGAGCAAATGAGATCAAAGTATGATGCTCGGCCAGTTCACAAGCCAATTGCTGCCCGGGAAGGAAATT
CGCACACAGTTATACTCTTCAATCCATCAGAACAGACGAGAGAGGAGGTGGTGACGGTTGTTGTTAACCGCGCTGA
AATCTCGGTTTTGGACTCAAACTGGACTTGTGTCCCTAGCCAAATTTCTCCTGAAGTGCAGCATGACGATACCAAA
CTATTCACCGGCAGACATCGCCTTTACTGGAAAGCTTCCATCCCAGCTCTTGGTCTGAGAACATATTTCATTGCTA
ATGGGAATGTCGAGTGTGAGAAAGCTACTCCGTCTAAACTCAAATACGCTTCTGAGTTTGACCCATTTCCTTGTCC
TCCTCCATATTCCTGCTCCAAACTGGACAACGACGTTACTGAGATCCGAAATGAACATCAGACTCTTGTGTTTGAT
GTGAAGAACGGATCACTGCGGAAGATAGTCCATAGAAACGGATCAGAGACTGTTGTGGGAGAAGAGATAGGTATGT
ACTCTAGTCCAGAGAGTGGAGCTTACCTGTTCAAACCAGATGGTGAAGCTCAGCCAATTGTTCAACCTGATGGACA
TGTAGTCACCTCTGAGGGTCTGCTGGTTCAAGAAGTCTTCTCTTACCCTAAAACCAAATGGGAGAAATCACCCCTC
TCTCAGAAAACTCGTCTTTACACTGGAGGTAATACGCTTCAGGATCAAGTGGTCGAGATAGAATATCATGTTGAGC
TTCTTGGTAATGATTTTGATGACCGGGAATTGATTGTCCGGTACAAGACTGATGTTGACAACAAGAAGGTCTTCTA
TTCAGATCTCAATGGTTTCCAAATGAGCAGGAGAGAAACTTATGATAAGATCCCTCTTCAAGGAAACTACTACCCA
ATGCCATCTCTCGCATTTATCCAAGGATCCAATGGTCAGAGATTCTCCGTGCACTCTCGTCAATCTCTCGGTGTTG

FIG. 27 Cont.

CAAGCCTCAAAGAGGGTTGGTTGGAGATTATGCTGGACAGACGGTTGGTTCGTGATGACGGACGGGGTCTAGGGCA
AGGTGTGATGGATAACCGCGCAATGACCGTGGTATTTCACCTTCTTGCGGAATCTAACATTTCTCAAGCAGACCCT
GCTTCCAACACTAACCCGAGGAACCCTTCGCTTCTCTCTCACCTCATAGGTGCTCACTTAAACTACCCCATAAACA
CATTCATTGCCAAGAAACCGCAAGACATATCTGTGCGTGTTCCACAATACGGTTCCTTTGCTCCTTTAGCCAAACC
GTTACCATGTGACCTCCACATTGTAAATTTCAAGGTTCCTCGTCCATCCAAATACTCTCAGCAATTGGAAGAAGAC
AAGCCAAGGTTCGCTCTTATCCTCAATAGACGAGCTTGGGATTCAGCTTATTGCCATAAAGGAAGACAAGTAAACT
GCACAAGCATGGCTAATGAACCAGTAAACTTTTCCGACATGTTCAAAGATCTTGCAGCTTCAAAGGTAAAACCAAC
TTCACTGAATCTCTTGCAAGAAGATATGGAGATTCTTGGGTACGATGACCAAGAGCTACCTCGAGATAGTTCACAG
CCACGGGAAGGACGTGTCTCGATCTCTCCCATGGAAATACGAGCTTATAAGCTTGAACTGCGACCTCACAAGTGAA
CCTGCTGAAGATCCGCTAGAGTCCGCAAAAATCACCAGTCTCTCTCTACAAATCTATCTCTCTCTATTTTTCTCCA
GAATAATGTGTGAGTAGTTCCCAGATAAGGGAATTAGGGTTCTTATAGGGTTTCGCTCATGTGTTGAGCATATAAG
AAACCCTTAGTATGTATTTGTATTTGTAAAATACTTCTATCAATAAAATTTCTAATCCTAAAACCAAAATCCCGCG
AGAGACCTCTTAATTAA

FIG. 27 Cont.

AGATCTAATCTAACCAATTACGATACGCTTTGGGTACACTTGATTTTTGTTTCAGTGGTTACATATATCTTGTTTT
ATATGCTATCTTTAAGGATCTGCACAAAGATTATTTGTTGATGTTCTTGATGGGGCTCAGAAGATTTGATATGATA
CACTCTAATCTTTAGGAGATACCAGCCAGGATTATATTCAGTAAGACAATCAAATTTTACGTGTTCAAACTCGTTA
TCTTTTCATTCAAAGGATGAGCCAGAATCTTTATAGAATGATTGCAATCGAGAATATGTTCGGCCGATATGCCTTT
GTTGGCTTCAATATTCTACATATCACACAAGAATCGACCGTATTGTACCCTCTTTCCATAAAGGAAAACACAATAT
GCAGATGCTTTTTTCCCACATGCAGTAACATATAGGTATTCAAAAATGGCTAAAAGAAGTTGGATAACAAATTGAC
AACTATTTCCATTTCTGTTATATAAATTTCACAACACACAAAAGCCCGTAATCAAGAGTCTGCCCATGTACGAAAT
AACTTCTATTATTTGGTATTGGGCCTAAGCCCAGCTCAGAGTACGTGGGGGTACCACATATAGGAAGGTAACAAAA
TACTGCAAGATAGCCCCATAACGTACCAGCCTCTCCTTACCACGAAGAGATAAGATATAAGACCCACCCTGCCACG
TGTCACATCGTCATGGTGGTTAATGATAAGGGATTACATCCTTCTATGTTTGTGGACATGATGCATGTAATGTCAT
GAGCCACAGGATCCAATGGCCACAGGAACGTAAGAATGTAGATAGATTTGATTTTGTCCGTTAGATAGCAAACAAC
ATTATAAAAGGTGTGTATCAATAGGAACTAATTCACTCATTGGATTCATAGAAGTCCATTCCTCCTAAGTATCTAG
AAACCATGG

FIG. 28

CCATGGCGAGAGGGAGCAGATCAGTGGGTAGCAGCAGCAGCAAATGGAGGTACTGCAACCCTTCCTATTACTTGAA
GCGCCCAAAGCGTCTTGCTCTGCTCTTCATCGTTTTCGTTTGTGTCTCTTTCGTTTTCTGGGACCGTCAAACTCTC
GTCAGAGAGCACCAGGTTGAAATTTCTGAGCTGCAGAAAGAAGTGACTGATTTGAAAAATTTGGTGGATGATTTAA
ATAACAAACAAGGTGGTACCTCTGGGAAAACTGACTTGGGGACCATGGATTCCAATTCAGGCGCCGTCGTTGATAT
CACAACTAAAGATCTATACGATAGGATTGAGTTTCTTGATACAGATGGTGGTCCATGGAAACAAGGTTGGAGAGTT
ACGTATAAAGACGATGAGTGGGAGAAAGAGAAGCTCAAAATCTTCGTTGTTCCTCATTCTCATAACGATCCTGGTT
GGAAATTGACTGTAGAGGAGTATTATCAGAGACAATCCAGACATATTCTTGACACCATTGTTGAGACTTTATCTAA
GGTATGACGAAAGTTTTTGCTTTTGGTTTTAATATTTTAATTCTCTCCCATGGTTATCCCGTGAACAATCTTAAAT
GTCTTAAAATTCTCATGACGTCATTAAACTCTATAACCAAACTTCTTTGCTGGGTTCTGTTTTTTTTTAGTTTCGT
GATGAAACAGAGTTCTAGAAGTTCGTTCTTTTGGAAAATTTGAAGTCTTTGGAGCTAAAGTTTGTTTTTTTATTAC
TGGGTTTTGAGATTGAAGGATAGCTAGAATCTTATTTGTGTGGGGGTTTGTTTTGAATATGTTTAATAGGATTCAA
GAAGAAAGTTTATATGGGAGGAGATGTCATATCTGGAGAGATGGTGGAGAGACGCTTCACCTAATAAACAAGAAGC
TTTGACTAAATTGGTTAAGGATGGGCAGCTAGAGATTGTTGGAGGTGGCTGGGTTATGAATGATGAGGCTAATTCA
CATTATTTTGCCATAATTGAACAGATAGCAGAGGGTAATATGTGGCTGAATGACACAATTGGGGTTATTCCTAAGA
ATTCTTGGGCTATAGATCCCTTTGGCTATTCATCAACCATGGCTTATCTTCTCCGGCGTATGGGTTTTGAAAACAT
GCTTATTCAAAGGACTCATTACGAGCTCAAGAAAGACCTTGCCCAGCATAAGAATCTTGAATATATTTGGCGTCAG
AGCTGGGATGCTATGGAAACCACAGATATCTTTGTTCATATGATGCCGTTTTATTCATACGATATCCCACACACTT
GTGGACCAGAGCCTGCAATTTGCTGTCAGTTTGATTTCGCTCGGATGCGGGGATTTAAGTATGAACTTTGTCCATG
GGGAAAGCACCCAGTGGAGACCACACTAGAAAATGTGCAGGAGAGGGCATTAAAGCTTCTGGATCAATACAGGAAA
AAATCCACTCTATATCGAACTAATACACTTCTTATACCTCTTGGAGATGATTTTAGGTACATTAGTATCGATGAAG
CCGAGGCTCAGTTCCGTAACTACCAGATGTTGTTTGATCACATCAACTCTAATCCTAGTCTAAACGCAGAAGCAAA
GTTTGGTACTTTGGAGGATTATTTCAGAACAGTCCGAGAAGAAGCAGACAGAGTGAATTATTCTCGTCCTGGTGAG
GTTGGCTCTGGTCAGGTTGTTGGTTTCCCTTCTCTGTCAGGTGACTTCTTTACATATGCAGATAGGCAACAAGACT
ATTGGAGTGGTTATTATGTTTCAAGACCTTTCTTCAAAGCTGTTGATCGTGTGCTCGAGCATACCCTTCGTGGAGC
TGAGATCATGATGTCATTTCTGCTAGGTTATTGCCATCGAATTCAATGTGAGAAATTTCCAACAAGTTTTACGTAT
AAGTTGACTGCTGCAAGAAGAAATCTGGCTCTTTTCCAGCACCATGATGGGGTAACTGGAACTGCTAAGGATTATG

FIG. 29

TGGTACAAGATTACGGCACCCGGATGCATACTTCATTGCAAGACCTTCAGATCTTTATGTCTAAAGCAATCGAAGT
TCTTCTTGGGATCCGCCACGAGAAAGAAAAATCTGATCAATCCCCATCATTTTTCGAGGCAGAGCAAATGAGATCA
AAGTATGATGCTCGGCCAGTTCACAAGCCAATTGCTGCCCGGGAAGGAAATTCGCACACAGTTATACTCTTCAATC
CATCAGAACAGACGAGAGAGGAGGTGGTGACGGTTGTTGTTAACCGCGCTGAAATCTCGGTTTTGGACTCAAACTG
GACTTGTGTCCCTAGCCAAATTTCTCCTGAAGTGCAGCATGACGATACCAAACTATTCACCGGCAGACATCGCCTT
TACTGGAAAGCTTCCATCCCAGCTCTTGGTCTGAGAACATATTTCATTGCTAATGGGAATGTCGAGTGTGAGAAAG
CTACTCCGTCTAAACTCAAATACGCTTCTGAGTTTGACCCATTTCCTTGTCCTCCTCCATATTCCTGCTCCAAACT
GGACAACGACGTTACTGAGATCCGAAATGAACATCAGACTCTTGTGTTTGATGTGAAGAACGGATCACTGCGGAAG
ATAGTCCATAGAAACGGATCAGAGACTGTTGTGGGAGAAGAGATAGGTATGTACTCTAGTCCAGAGAGTGGAGCTT
ACCTGTTCAAACCAGATGGTGAAGCTCAGCCAATTGTTCAACCTGATGGACATGTAGTCACCTCTGAGGGTCTGCT
GGTTCAAGAAGTCTTCTCTTACCCTAAAACCAAATGGGAGAAATCACCCCTCTCTCAGAAAACTCGTCTTTACACT
GGAGGTAATACGCTTCAGGATCAAGTGGTCGAGATAGAATATCATGTTGAGCTTCTTGGTAATGATTTTGATGACC
GGGAATTGATTGTCCGGTACAAGACTGATGTTGACAACAAGAAGGTCTTCTATTCAGATCTCAATGGTTTCCAAAT
GAGCAGGAGAGAAACTTATGATAAGATCCCTCTTCAAGGAAACTACTACCCAATGCCATCTCTCGCATTTATCCAA
GGATCCAATGGTCAGAGATTCTCCGTGCACTCTCGTCAATCTCTCGGTGTTGCAAGCCTCAAAGAGGGTTGGTTGG
AGATTATGCTGGACAGACGGTTGGTTCGTGATGACGGACGGGGTCTAGGGCAAGGTGTGATGGATAACCGCGCAAT
GACCGTGGTATTTCACCTTCTTGCGGAATCTAACATTTCTCAAGCAGACCCTGCTTCCAACACTAACCCGAGGAAC
CCTTCGCTTCTCTCTCACCTCATAGGTGCTCACTTAAACTACCCCATAAACACATTCATTGCCAAGAAACCGCAAG
ACATATCTGTGCGTGTTCCACAATACGGTTCCTTTGCTCCTTTAGCCAAACCGTTACCATGTGACCTCCACATTGT
AAATTTCAAGGTTCCTCGTCCATCCAAATACTCTCAGCAATTGGAAGAAGACAAGCCAAGGTTCGCTCTTATCCTC
AATAGACGAGCTTGGGATTCAGCTTATTGCCATAAAGGAAGACAAGTAAACTGCACAAGCATGGCTAATGAACCAG
TAAACTTTTCCGACATGTTCAAAGATCTTGCAGCTTCAAAGGTAAAACCAACTTCACTGAATCTCTTGCAAGAAGA
TATGGAGATTCTTGGGTACGATGACCAAGAGCTACCTCGAGATAGTTCACAGCCACGGGAAGGACGTGTCTCGATC
TCTCCCATGGAAATACGAGCTTATAAGCTTGAACTGCGACCTCACAAGTGAACCTGCTGAAGATC

FIG. 29 Cont.

GGCGCGCCTCGAGGCGATCGCAGATCTCATTATACCGTTAGAAGCATAGTTAAAATCTAAAGCTTGTCGTTAATTC
TAGTCATTTTACATTGTTGGGTTCTACATTATTAATGAATTTTCTAATGCAAATACAGAATTTAAATCAAAATTGT
TGAATTATGCTAAACATGTAACATACGTATATCTCCGCCTTGTGTGTTGTATTAACTTGAAGTTATCATAAGAACC
ACAAATACACTAGTAAATCTATGAGAAGGCAGGTGGCAACACAAACAAGAGTATCTAAGATTTTCATTTGTGACTA
TAGGAATATAATATCTCTTATCTGATTTAATGAATCCACATGTTCACTTCTCATTTGTCCACAAGATCACAACTTT
ATCTTCAATATTCACAACTTGTTATATCCACCACAATTTCATTCTTTTCACTTAGCCCCACAAAATACTTTGTCCC
CTTATTTGCCACCTTTTGTATTTAATTTATTCTTGTGGAGCTAAGTGTTCATATTATTCTTCTTCTCAAAAAAACA
AAAACAAAAAAAAAAGAGAAGAAAACCATGGCGAGAGGGAGCAGATCAGTGGGTAGCAGCAGCAGCAAATGGAGGTA
CTGCAACCCTTCCTATTACTTGAAGCGCCCAAAGCGTCTTGCTCTGCTCTTCATCGTTTTCGTTTGTGTCTCTTTC
GTTTTCTGGGACCGTCAAACTCTCGTCAGAGAGCACCAGGTTGAAATTTCTGAGCTGCAGAAAGAAGTGACTGATT
TGAAAAATTTGGTGGATGATTTAAATAACAAACAAGGTGGTACCTCTGGGAAAACTGACTTGGGGACCATGGCTCT
AAGGTTGCATAGAAGGAACCATTTTTCGCCTAGAAATACGGATCTGTTCCCGGATTTGGCAAAAGATCGTGTGGTT
ATCGTCTTGTATGTGCATAATCGGGCTCAGTATTTTCGAGTCACAGTGGAAAGTTTGTCGAAGGTTAAAGGTATAA
GTGAGACATTGTTGATTGTTAGTCATGATGGTTACTTTGAAGAGATGAATAGGATTGTGGAGAGTATTAAGTTTTG
TCAAGTGAAACAGATTTTCTCGCCTTATTCGCCTCATATATATCGTACTAGCTTCCCGGGTGTGACCCTGAATGAT
TGTAAGAACAAGGGTGATGAGGCAAAGGGGCATTGTGAAGGTAATCCTGATCAGTATGGGAATCATCGGTCTCCGA
AGATTGTATCTTTGAAGCATCACTGGTGGTGGATGATGAACACTGTATGGGATGGGTTGGAAGAGACTAAAGGACA
TGAGGGGCATATCCTTTTCATTGAAGAAGATCATTTTCTGTTTCCTAATGCCTATCGTAACATACAGACTCTTACG
AGGCTGAAACCCGCAAAGTGTCCTGACTGTTTTGCTGCTAATTTAGCACCGTCTGATGTGAAGTCAAGAGGAGAAG
GGCTTGAAAGTTTGGTTGCAGAGAGAATGGGAAATGTTGGGTATTCTTTTAATAGAAGTGTGTGGGAGAATATTCA
TCAGAAGGCAAGAGAGTTTTGTTTCTTTGATGATTACAACTGGGATATAACGATGTGGGCAACGGTTTTCCCGTCG
TTTGGTTCCCCGGTGTACACATTGCGAGGGCCTAGGACTAGTGCGGTACACTTTGGAAAATGTGGGTTGCATCAAG

FIG. 30

GTAGAGGAGATGAGGGTGATTGCATCGATAATGGGGTCGTAAACATAGAAGTTAAGGAAACAGATAAAGTTGTGAA
CATAAAAGAAGGATGGGGAGTTCGGGTGTATAAGCATCAAGCGGGTTATAAAGCCGGTTTCGAAGGTTGGGGAGGT
TGGGGCGATGATAGGGACCGACATTTATGTTTGGATTTTGCCACTATGTATCGTTACAGCAGTAGCAGTGCATCTC
CATGAAACGGATCCGCTAGAGTCCGCAAAAATCACCAGTCTCTCTCTACAAATCTATCTCTCTCTATTTTTCTCCA
GAATAATGTGTGAGTAGTTCCCAGATAAGGGAATTAGGGTTCTTATAGGGTTTCGCTCATGTGTTGAGCATATAAG
AAACCCTTAGTATGTATTTGTATTTGTAAAATACTTCTATCAATAAAATTTCTAATCCTAAAACCAAAATCCCGCG
AGAGACCTCTTAATTAA

FIG. 30 Cont.

AGATCTCATTATACCGTTAGAAGCATAGTTAAAATCTAAAGCTTGTCGTTAATTCTAGTCATTTTACATTGTTGGG
TTCTACATTATTAATGAATTTTCTAATGCAAATACAGAATTTAAATCAAAATTGTTGAATTATGCTAAACATGTAA
CATACGTATATCTCCGCCTTGTGTGTTGTATTAACTTGAAGTTATCATAAGAACCACAAATACACTAGTAAATCTA
TGAGAAGGCAGGTGGCAACACAAACAAGAGTATCTAAGATTTTCATTTGTGACTATAGGAATATAATATCTCTTAT
CTGATTTAATGAATCCACATGTTCACTTCTCATTTGTCCACAAGATCACAACTTTATCTTCAATATTCACAACTTG
TTATATCCACCACAATTTCATTCTTTTCACTTAGCCCCACAAAATACTTTGTCCCCTTATTTGCCACCTTTTGTAT
TTAATTTATTCTTGTGGAGCTAAGTGTTCATATTATTCTTCTTCTCAAAAAAACAAAAACAAAAAAAAAGAGAAGA
AAACCATGG

FIG. 31

CCATGGCGAGAGGGAGCAGATCAGTGGGTAGCAGCAGCAGCAAATGGAGGTACTGCAACCCTTCCTATTACTTGAA
GCGCCCAAAGCGTCTTGCTCTGCTCTTCATCGTTTTCGTTTGTGTCTCTTTCGTTTTCTGGGACCGTCAAACTCTC
GTCAGAGAGCACCAGGTTGAAATTTCTGAGCTGCAGAAAGAAGTGACTGATTTGAAAAATTTGGTGGATGATTTAA
ATAACAAACAAGGTGGTACCTCTGGGAAAACTGACTTGGGGACCATGGCTCTAAGGTTGCATAGAAGGAACCATTT
TTCGCCTAGAAATACGGATCTGTTCCCGGATTTGGCAAAAGATCGTGTGGTTATCGTCTTGTATGTGCATAATCGG
GCTCAGTATTTTCGAGTCACAGTGGAAAGTTTGTCGAAGGTTAAAGGTATAAGTGAGACATTGTTGATTGTTAGTC
ATGATGGTTACTTTGAAGAGATGAATAGGATTGTGGAGAGTATTAAGTTTTGTCAAGTGAAACAGATTTTCTCGCC
TTATTCGCCTCATATATATCGTACTAGCTTCCCGGGTGTGACCCTGAATGATTGTAAGAACAAGGGTGATGAGGCA
AAGGGGCATTGTGAAGGTAATCCTGATCAGTATGGGAATCATCGGTCTCCGAAGATTGTATCTTTGAAGCATCACT
GGTGGTGGATGATGAACACTGTATGGGATGGGTTGGAAGAGACTAAAGGACATGAGGGGCATATCCTTTTCATTGA
AGAAGATCATTTTCTGTTTCCTAATGCCTATCGTAACATACAGACTCTTACGAGGCTGAAACCCGCAAAGTGTCCT
GACTGTTTTGCTGCTAATTTAGCACCGTCTGATGTGAAGTCAAGAGGAGAAGGGCTTGAAAGTTTGGTTGCAGAGA
GAATGGGAAATGTTGGGTATTCTTTTAATAGAAGTGTGTGGGAGAATATTCATCAGAAGGCAAGAGAGTTTTGTTT
CTTTGATGATTACAACTGGGATATAACGATGTGGGCAACGGTTTTCCCGTCGTTTGGTTCCCCGGTGTACACATTG
CGAGGGCCTAGGACTAGTGCGGTACACTTTGGAAAATGTGGGTTGCATCAAGGTAGAGGAGATGAGGGTGATTGCA
TCGATAATGGGGTCGTAAACATAGAAGTTAAGGAAACAGATAAAGTTGTGAACATAAAAGAAGGATGGGGAGTTCG
GGTGTATAAGCATCAAGCGGGTTATAAAGCCGGTTTCGAAGGTTGGGGAGGTTGGGGCGATGATAGGGACCGACAT
TTATGTTTGGATTTTGCCACTATGTATCGTTACAGCAGTAGCAGTGCATCTCCATGAAACGGATCC

FIG. 32

GGATCCGCTAGAGTCCGCAAAAATCACCAGTCTCTCTCTACAAATCTATCTCTCTCTATTTTTCTCCAGAATAATG
TGTGAGTAGTTCCCAGATAAGGGAATTAGGGTTCTTATAGGGTTTCGCTCATGTGTTGAGCATATAAGAAACCCTT
AGTATGTATTTGTATTTGTAAAATACTTCTATCAATAAAATTTCTAATCCTAAAACCAAAATCCCGCGAGAGACCT
CTTAATTAA

FIG. 33

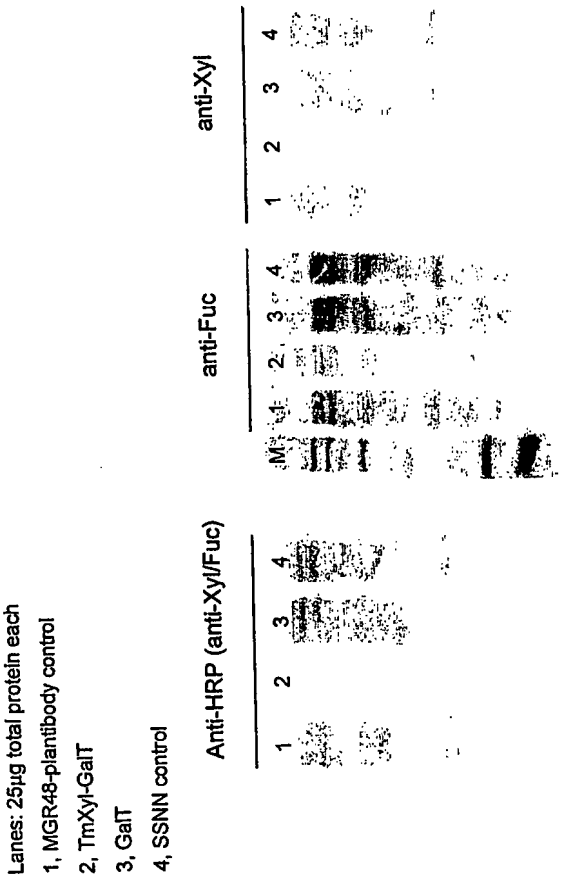
Lanes: 25µg total protein each
1, MGR48-plantibody control
2, TmXyl-GalT
3, GalT
4, SSNN control
Anti-HRP (anti-Xyl/Fuc)
1 2 3 4
anti-Fuc
M 1 2 3 4
anti-Xyl
1 2 3 4

FIG. 34

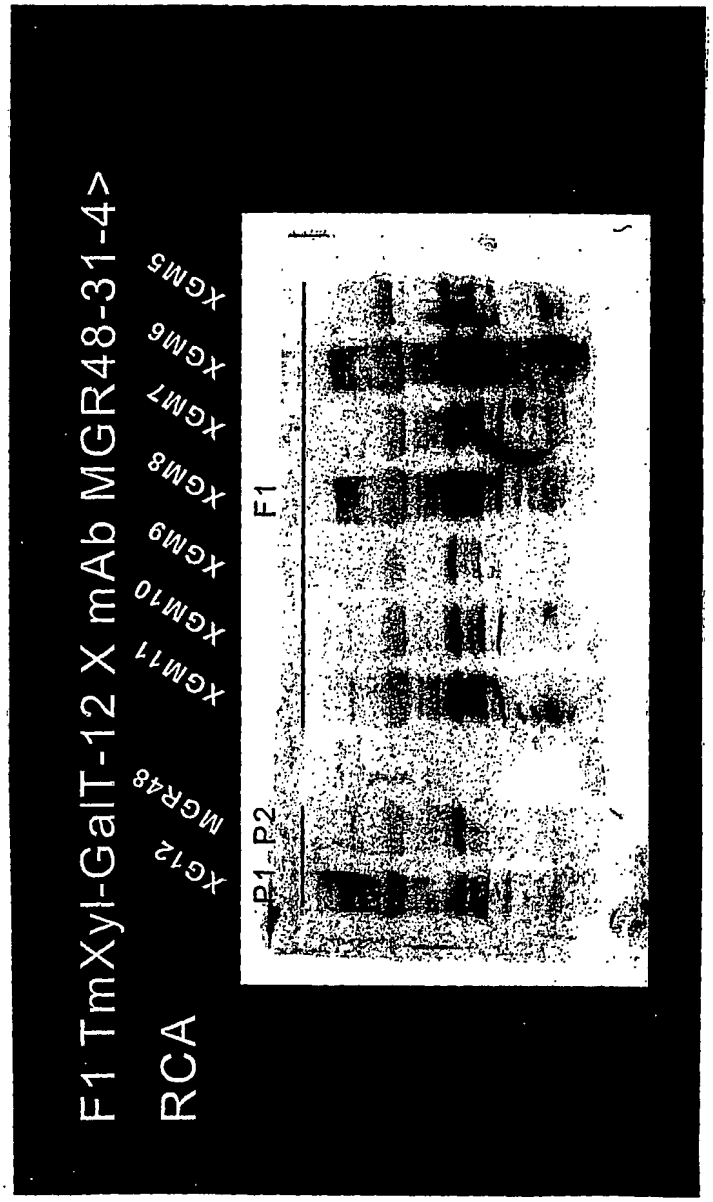
F1 TmXyl-GalT-12 X mAb MGR48-31-4>
RCA
XG12
MGR48
XGM11
XGM10
XGM9
XGM8
XGM7
XGM6
XGM5
F1
P1 P2

FIG. 35

Lanes 1, 2 & 3: 300 ng MGR48 IgG

1, MGR48 hybridoma

2, MGR48 tobacco

3, MGR48 TmXyl-GalT

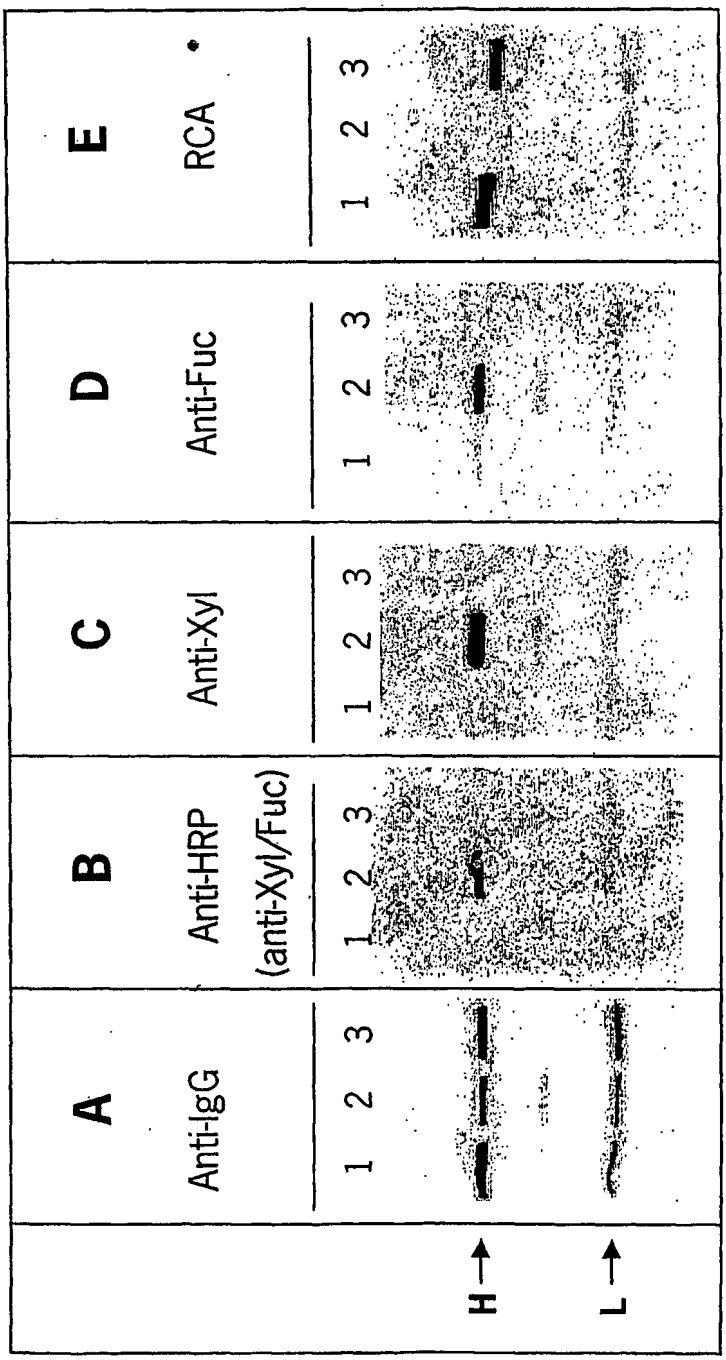

FIG. 36

ATGGGCATCAAGATGGAGACACATTCTCAGGTCTTTGTATACATGTTGCTGTGGTTGTCTGGTGTCGACATGAAGCACTTCAAATCTTCCCTCACT
CACACCGTCAAGAGCCGAGACGAGCCAACTCCGGATCAATGCCCTGCATTGAAGGAAAGCGAAGCGGACATCGACACCGTGGCGATATACCCAACT
TTTGATTTTCAGCCGAGCTGGTTGCGTACAAAGGAATTTTGGGACAAGTCCTTCGAGGATCGGTATGAAAGAATTCATAACGACACTACACGGCCT
AGACTGAAGGTAATCGTGGTTCCTCACTCACACAACGACCCGGGATGGCTGAAGACGTTTGAACAGTACTTCGAGTGGAAGACCAAGAACATTATC
AACAACATAGTGAACAAACTGCACCAGTACCCCAACATGACCTTCATTTGGACCGAGATATCGTTTCTGAATGCCTGGTGGGAAAGGTCGCACCCT
GTCAAACAAAAGGCATTGAAAAAACTTATCAAAGAAGGTCGTCTCGAGATCACGACGGGCGGCTGGGTGATGCCGGACGAAGCCTGCACGCATATC
TATGCGCTAATTGACCAGTTTATTGAAGGACATCACTGGGTGAAAACTAATCTCGGCGTCATCCCGAAGACAGGATGGTCTATTGACCCCTTCGGC
CACGGGGCCACTGTGCCTTACCTGCTAGACCAGAGCGGCCTTGAGGGAACCATTATACAGAGAATCCATTATGCGTGGAAACAGTGGCTGGCGGAG
CGACAGATTGAGGAGTTTTACTGGCTGGCGAGTTGGGCTACTACGAAGCCGTCCATGATAGTGCACAATCAGCCGTTTGATATTTATTCAATAAAA
AGCACGTGTGGCCCGCACCCTTCAATTTGTCTCAGTTTCGACTTCAGGAAGATTCCCGGCGAATATTCTGAATACACAGCTAAGCACGAAGACATC
ACGGAACACAACTTGCACAGCAAGGCAAAGACTTTGATAGAGGAGTACGACCGTATCGGGTCCCTGACTCCACACAACGTGGTGCTGGTGCCGCTC
GGAGACGACTTCAGATACGAGTACAGCGTCGAGTTTGATGCCCAATACGTCAATTATATGAAAATGTTTAACTACATCAATGCTCACAAGGAAATC
TTCAACGCTGACGTACAGTTCGGAACTCCTCTCGATTACTTTAACGCCATGAAAGAAAGACATCAAAATATACCCAGCTTAAAGGGAGATTTCTTC
GTTTACTCCGATATTTTCAGCGAAGGTAAACCAGCGTACTGGTCAGGTTACTACACTACTAGACCCTACCAAAAAATCCTCGCCCGTCAGTTCGAA
CACCAACTGCGATCGGCAGAGATTTTATTCACCCTTGTATCGAACTACATCAGACAGATGGGTCGCCAAGGAGAGTTCGGAGCTTCTGAGAAAAAG
TTAGAAAAATCTTACGAGCAGCTTATCTATGCTCGACGGAACTTGGGTCTGTTTCAACATCACGATGCGATTACTGGAACATCAAAGTCCAGTGTG
ATGCAAGATTACGGAACCAAACTGTTCACAAGTCTGTATCACTGCATCCGCCTGCAGGAGGCCGCGCTCACCACCATCATGTTGCCTGACCAGTCG
TTGCACTCGCAGAGCATTATACAAAGCGAGGTTGAGTGGGAAACTTACGGAAAACCGCCCAAGAAGCTGCAAGTGTCCTTCATTGACAAGAAGAAA
GTTATACTTTTTAATCCGTTGGCTGAGACTCGAACTGAAGTGGTCACGGTTAGATCCAACACGTCCAACATCCGGGTGTACGATACACACAAGAGG
AAGCACGTCTTGTATCAGATAATGCCCAGCATCACAATCCAAGACAACGGCAAGAGTATCGTAAGCGACACCACGTTCGACATAATGTTCGTGGCC
ACCATCCCGCCCCTCACCTCCATCTCGTACAAGCTGCAGGAGCACACCAACACTTCCCACCACTGCGTCATTTTCTGCAACAACTGCGAACAATAC
CAGAAATCCAATGTGTTCCAAATTAAGAAAATGATGCCTGGTGACATACAATTAGAAAATGCAGTGCTAAAACTTCTCGTTAATAGGAACACCGGC
TTTCTGAGACAAGTCTATAGAAAGGACATCCGGAAGAGAACTGTCGTTGACGTACAATTCGGCGCATATCAAAGTGCCCAAAGACATTCTGGTGCT
TACCTCTTCATGCCTCATTACGACTCACCTGAGAAGAATGTTCTGCATCCCTACACTAATCAGAACAACATGCAAGATGATAACATAATCATAGTG
TCCGGACCTATTTCTACGGAAATCACGACCATGTACTTGCCCTTCTTGGTGCACACTATTAGGATATACAACGTGCCGGACCCGGTACTGTCGCGT
GCTATTCTATTAGAGACCGATGTAGATTTCGAGGCGCCACCTAAGAACAGAGAGACTGAGTTATTTATGAGATTACAGACTGATATACAAAACGGT
GACATTCCCGAATTTTACACCGATCAGAACGGATTCCAGTACCAAAAGAGGGTCAAAGTGAATAAACTAGGAATAGAAGCTAATTACTACCCGATC
ACTACCATGGCGTGCCTGCAAGACGAGGAGACCCGGCTCACTCTGCTGACGAACCACGCTCAAGGCGCTGCTGCATACGAACCAGGACGCTTAGAA

FIG. 37

GTCATGCTCGATCGTCGAACTCTTTATGATGACTTCAGAGGAATCGGTGAAGGAGTAGTCGATAACAAACCGACGACTTTCCAGAACTGGATTTTA
ATTGAATCCATGCCAGGCGTGACGCGAGCCAAGAGAGACACTAGTGAACCAGGTTTCAAATTTGTTAATGAACGTCGTTTTGGCCCCGGCCAGAAG
GAAAGCCCTTACCAAGTACCGTCGCAGACTGCGGACTACCTGAGCAGGATGTTCAATTACCCGGTGAACGTGTACCTGGTGGACACTAGCGAGGTT
GGCGAGATCGAGGTGAAGCCGTACCAGTCGTTCCTGCAGAGCTTCCCGCCCGGCATCCACCTGGTCACCCTGCGCACCATCACCGACGACGTGCTC
GAACTCTTCCCCAGCAACGAAAGCTACATGGTACTGCACCGACCAGGATACAGCTGCGCTGTCGGAGAGAAGCCAGTCGCCAAGTCTCCCAAGTTT
TCGTCCAAAACCAGGTTCAATGGTCTGAACATTCAGAACATCACTGCAGTCAGCCTGACCGGCCTGAAGTCACTCCGACCTCTCACAGGTCTGAGT
GACATCCACCTGAACGCTATGGAGGTAAAAACTTACAAGATCAGGTTTAAGGACGAGCTTTAA

FIG. 37 Cont.

MGIKMETHSQVFVYMLLWLSGVDMKHFKSSLTHTVKSRDEPTPDQCPALKESEADIDTVAIYPTFDFQPSWLRTKEFWDKSFEDRYERIHNDTTRP
RLKVIVVPHSHNDPGWLKTFEQYFEWKTKNIINNIVNKLHQYPNMTFIWTEISFLNAWWERSHPVKQKALKKLIKEGRLEITTGGWVMPDEACTHI
YALIDQFIEGHHWVKTNLGVIPKTGWSIDPFGHGATVPYLLDQSGLEGTIIQRIHYAWKQWLAERQIEEFYWLASWATTKPSMIVHNQPFDIYSIK
STCGPHPSICLSFDFRKIPGEYSEYTAKHEDITEHNLHSKAKTLIEEYDRIGSLTPHNVVLVPLGDDFRYEYSVEFDAQYVNYMKMFNYINAHKEI
FNADVQFGTPLDYFNAMKERHQNIPSLKGDFFVYSDIFSEGKPAYWSGYYTTRPYQKILARQFEHQLRSAEILFTLVSNYIRQMGRQGEFGASEKK
LEKSYEQLIYARRNLGLFQHHDAITGTSKSSVMQDYGTKLFTSLYHCIRLQEAALTTIMLPDQSLHSQSIIQSEVEWETYGKPPKKLQVSFIDKKK
VILFNPLAETRTEVVTVRSNTSNIRVYDTHKRKHVLYQIMPSITIQDNGKSIVSDTTFDIMFVATIPPLTSISYKLQEHTNTSHHCVIFCNNCEQY
QKSNVFQIKKMMPGDIQLENAVLKLLVNRNTGFLRQVYRKDIRKRTVVDVQFGAYQSAQRHSGAYLFMPHYDSPEKNVLHPYTNQNNMQDDNIIIV
SGPISTEITTMYLPFLVHTIRIYNVPDPVLSRAILLETDVDFEAPPKNRETELFMRLQTDIQNGDIPEFYTDQNGFQYQKRVKVNKLGIEANYYPI
TTMACLQDEETRLTLLTNHAQGAAAYEPGRLEVMLDRRTLYDDFRGIGEGVVDNKPTTFQNWILIESMPGVTRAKRDTSEPGFKFVNERRFGPGQK
ESPYQVPSQTADYLSRMFNYPVNVYLVDTSEVGEIEVKPYQSFLQSFPPGIHLVTLRTITDDVLELFPSNESYMVLHRPGYSCAVGEKPVAKSPKF
SSKTRFNGLNIQNITAVSLTGLKSLRPLTGLSDIHLNAMEVKTYKIRFKDEL

FIG. 38

ATGGGCATCAAGATGGAGACACATTCTCAGGTCTTTGTATACATGTTGCTGTGGTTGTCTGGTGTCGACATGCAGTCCTCCGGGGAGCTCCGGACC
GGAGGGGCCCGGCCGCCGCCTCCTCTAGGCGCCTCCTCCCAGCCGCGCCCGGGTGGCGACTCCAGCCCAGTCGTGGATTCTGGCCCTGGCCCCGCT
AGCAACTTGACCTCGGTCCCAGTGCCCCACACCACCGCACTGTCGCTGCCCGCCTGCCCTGAGGAGTCCCCGCTGCTTGTGGGCCCCATGCTGATT
GAGTTTAACATGCCTGTGGACCTGGAGCTCGTGGCAAAGCAGAACCCAAATGTGAAGATGGGCGGCCGCTATGCCCCCAGGGACTGCGTCTCTCCT
CACAAGGTGGCCATCATCATTCCATTCCGCAACCGGCAGGAGCACCTCAAGTACTGGCTATATTATTTGCACCCAGTCCTGCAGCGCCAGCAGCTG
GACTATGGCATCTATGTTATCAACCAGGCGGGAGACACTATATTCAATCGTGCTAAGCTCCTCAATGTTGGCTTTCAAGAAGCCTTGAAGGACTAT
GACTACACCTGCTTTGTGTTTAGTGACGTGGACCTCATTCCAATGAATGACCATAATGCGTACAGGTGTTTTTCACAGCCACGGCACATTTCCGTT
GCAATGGATAAGTTTGGATTCAGCCTACCTTATGTTCAGTATTTTGGAGGTGTCTCTGCTCTAAGTAAACAACAGTTTCTAACCATCAATGGATTT
CCTAATAATTATTGGGGCTGGGGAGGAGAAGATGATGACATTTTTAACAGATTAGTTTTTAGAGGCATGTCTATATCTCGCCCAAATGCTGTGGTC
GGGAGGTGTCGCATGATCCGCCACTCAAGAGACAAGAAAAATGAACCCAATCCTCAGAGGTTTGACCGAATTGCACACACAAAGGAGACAATGCTC
TCTGATGGTTTGAACTCACTCACCTACCAGGTGCTGGATGTACAGAGATACCCATTGTATACCCAAATCACAGTGGACATCGGGACACCGAGCAAG
GACGAGCTTTAG

FIG. 39

MGIKMETHSQVFVYMLLWLSGVDMQSSGELRTGGARPPPPLGASSQPRPGGDSSPVVDSGPGPASNLTSVPVPHTTALSLPACPEESPLLVGPMLI
EFNMPVDLELVAKQNPNVKMGGRYAPRDCVSPHKVAIIIPFRNRQEHLKYWLYYLHPVLQRQQLDYGIYVINQAGDTIFNRAKLLNVGFQEALKDY
DYTCFVFSDVDLIPMNDHNAYRCFSQPRHISVAMDKFGFSLPYVQYFGGVSALSKQQFLTINGFPNNYWGWGGEDDDIFNRLVFRGMSISRPNAVV
GRCRMIRHSRDKKNEPNPQRFDRIAHTKETMLSDGLNSLTYQVLDVQRYPLYTQITVDIGTPSKDEL

FIG. 40

ATGGGCATCAAGATGGAGACACATTCTCAGGTCTTTGTATACATGTTGCTGTGGTTGTCTGGTGTCGACATGGGACAGATGCCTGTGGCTGCTGTA
GTGGTTATGGCCTGCAGTCGTGCAGACTATCTTGAAAGGACTGTTAAATCAGTTTTAACATATCAAACTCCCGTTGCTTCAAAATATCCTCTATTT
ATATCTCAGGATGGATCTGATCAAGCTGTCAAGAGCAAGTCATTGAGCTATAATCAATTAACATATATGCAGCACTTGGATTTTGAACCAGTGGTC
ACTGAAAGGCCTGGCGAACTGACTGCGTACTACAAGATTGCACGTCACTACAAGTGGGCACTGGACCAGTTGTTTTACAAACACAAATTTAGTCGA
GTGATTATACTAGAAGATGATATGGAAATTGCTCCAGACTTCTTTGATTACTTTGAGGCTGCAGCTAGTCTCATGGATAGGGATAAAACCATTATG
GCTGCTTCATCATGGAATGATAATGGACAGAAGCAGTTTGTGCATGATCCCTATGCGCTATACCGATCAGATTTTTTTCCTGGCCTTGGGTGGATG
CTCAAGAGATCGACTTGGGATGAGTTATCACCAAAGTGGCCAAAGGCTTACTGGGATGATTGGCTGAGACTAAAGGAAAACCATAAAGGCCGCCAA
TTCATTCGACCGGAAGTCTGTAGAACATACAATTTTGGTGAACATGGGTCTAGTTTGGGACAGTTTTTCAGTCAGTATCTGGAACCTATAAAGCTA
AACGATGTGACGGTTGACTGGAAAGCAAAGGACCTGGGATACCTGACAGAGGGAAACTATACCAAGTACTTTTCTGGCTTAGTGAGACAAGCACGA
CCAATTCAAGGTTCTGACCTTGTCTTAAAGGCTCAAAACATAAAGGATGATGTTCGTATCCGGTATAAAGACCAAGTAGAGTTTGAACGCATTGCA
GGGGAATTTGGTATATTTGAAGAATGGAAGGATGGTGTGCCTCGAACAGCATATAAAGGAGTAGTGGTGTTTCGAATCCAGACAACAAGACGTGTA
TTCCTGGTTGGGCCAGATTCTGTAATGCAGCTTGGAATTCGAAATTCCAAGGACGAGCTTTGA

FIG. 41

MGIKMETHSQVFVYMLLWLSGVDMGQMPVAAVVVMACSRADYLERTVKSVLTYQTPVASKYPLFISQDGSDQAVKSKSLSYNQLTYMQHLDFEPVV
TERPGELTAYYKIARHYKWALDQLFYKHKFSRVIILEDDMEIAPDFFDYFEAAASLMDRDKTIMAASSWNDNGQKQFVHDPYALYRSDFFPGLGWM
LKRSTWDELSPKWPKAYWDDWLRLKENHKGRQFIRPEVCRTYNFGEHGSSLGQFFSQYLEPIKLNDVTVDWKAKDLGYLTEGNYTKYFSGLVRQAR
PIQGSDLVLKAQNIKDDVRIRYKDQVEFERIAGEFGIFEEWKDGVPRTAYKGVVVFRIQTTRRVFLVGPDSVMQLGIRNSKDEL

FIG. 42

ATGGGCATCAAGATGGAGACACATTCTCAGGTCTTTGTATACATGTTGCTGTGGTTGTCTGGTGTCGACATGGCTCTAAGGTTGCATAGAAGGAAC
CATTTTTCGCCTAGAAATACGGATCTGTTCCCGGATTTGGCAAAAGATCGTGTGGTTATCGTCTTGTATGTGCATAATCGGGCTCAGTATTTTCGA
GTCACAGTGGAAAGTTTGTCGAAGGTTAAAGGTATAAGTGAGACATTGTTGATTGTTAGTCATGATGGTTACTTTGAAGAGATGAATAGGATTGTG
GAGAGTATTAAGTTTTGTCAAGTGAAACAGATTTTCTCGCCTTATTCGCCTCATATATATCGTACTAGCTTCCCGGGTGTGACCCTGAATGATTGT
AAGAACAAGGGTGATGAGGCAAAGGGGCATTGTGAAGGTAATCCTGATCAGTATGGGAATCATCGGTCTCCGAAGATTGTATCTTTGAAGCATCAC
TGGTGGTGGATGATGAACACTGTATGGGATGGGTTGGAAGAGACTAAAGGACATGAGGGGCATATCCTTTTCATTGAAGAAGATCATTTTCTGTTT
CCTAATGCCTATCGTAACATACAGACTCTTACGAGGCTGAAACCCGCAAAGTGTCCTGACTGTTTTGCTGCTAATTTAGCACCGTCTGATGTGAAG
TCAAGAGGAGAAGGGCTTGAAAGTTTGGTTGCAGAGAGAATGGGAAATGTTGGGTATTCTTTTAATAGAAGTGTGTGGGAGAATATTCATCAGAAG
GCAAGAGAGTTTTGTTTCTTTGATGATTACAACTGGGATATAACGATGTGGGCAACGGTTTTCCCGTCGTTTGGTTCCCCGGTGTACACATTGCGA
GGGCCTAGGACTAGTGCGGTACACTTTGGAAAATGTGGGTTGCATCAAGGTAGAGGAGATGAGGGTGATTGCATCGATAATGGGGTCGTAAACATA
GAAGTTAAGGAAACAGATAAAGTTGTGAACATAAAAGAAGGATGGGGAGTTCGGGTGTATAAGCATCAAGCGGGTTATAAAGCCGGTTTCGAAGGT
TGGGGAGGTTGGGGCGATGATAGGGACCGACATTTATGTTTGGATTTTGCCACTATGTATCGTTACAGCAGTAGCAGTGCATCTCCAAAGGACGAG
CTTTGA

FIG. 43

MGIKMETHSQVFVYMLLWLSGVDMALRLHRRNHFSPRNTDLFPDLAKDRVVIVLYVHNRAQYFRVTVESLSKVKGISETLLIVSHDGYFEEMNRIV
ESIKFCQVKQIFSPYSPHIYRTSFPGVTLNDCKNKGDEAKGHCEGNPDQYGNHRSPKIVSLKHHWWWMMNTVWDGLEETKGHEGHILFIEEDHFLF
PNAYRNIQTLTRLKPAKCPDCFAANLAPSDVKSRGEGLESLVAERMGNVGYSFNRSVWENIHQKAREFCFFDDYNWDITMWATVFPSFGSPVYTLR
GPRTSAVHFGKCGLHQGRGDEGDCIDNGVVNIEVKETDKVVNIKEGWGVRVYKHQAGYKAGFEGWGGWGDDRDRHLCLDFATMYRYSSSSASPKDE
L

FIG. 44

ATGCTGAAGAAGCAGTCTGCAGGGCTTGTGCTGTGGGGCGCTATCCTCTTTGTGGCCTGGAATGCCCTGCTGCTCCTCTTCTTCTGGACGCGCCCA
GCACCTGGCAGGCCACCCTCAGTCAGCGCTCTCGATGGCGACCCCGCCAGCCTCACCCGGGAAGTCGACATGCAGTCCTCCGGGGAGCTCCGGACC
GGAGGGGCCCGGCCGCCGCCTCCTCTAGGCGCCTCCTCCCAGCCGCGCCCGGGTGGCGACTCCAGCCCAGTCGTGGATTCTGGCCCTGGCCCCGCT
AGCAACTTGACCTCGGTCCCAGTGCCCCACACCACCGCACTGTCGCTGCCCGCCTGCCCTGAGGAGTCCCCGCTGCTTGTGGGCCCCATGCTGATT
GAGTTTAACATGCCTGTGGACCTGGAGCTCGTGGCAAAGCAGAACCCAAATGTGAAGATGGGCGGCCGCTATGCCCCCAGGGACTGCGTCTCTCCT
CACAAGGTGGCCATCATCATTCCATTCCGCAACCGGCAGGAGCACCTCAAGTACTGGCTATATTATTTGCACCCAGTCCTGCAGCGCCAGCAGCTG
GACTATGGCATCTATGTTATCAACCAGGCGGGAGACACTATATTCAATCGTGCTAAGCTCCTCAATGTTGGCTTTCAAGAAGCCTTGAAGGACTAT
GACTACACCTGCTTTGTGTTTAGTGACGTGGACCTCATTCCAATGAATGACCATAATGCGTACAGGTGTTTTTCACAGCCACGGCACATTTCCGTT
GCAATGGATAAGTTTGGATTCAGCCTACCTTATGTTCAGTATTTTGGAGGTGTCTCTGCTCTAAGTAAACAACAGTTTCTAACCATCAATGGATTT
CCTAATAATTATTGGGGCTGGGGAGGAGAAGATGATGACATTTTTAACAGATTAGTTTTTAGAGGCATGTCTATATCTCGCCCAAATGCTGTGGTC
GGGAGGTGTCGCATGATCCGCCACTCAAGAGACAAGAAAAATGAACCCAATCCTCAGAGGTTTGACCGAATTGCACACACAAAGGAGACAATGCTC
TCTGATGGTTTGAACTCACTCACCTACCAGGTGCTGGATGTACAGAGATACCCATTGTATACCCAAATCACAGTGGACATCGGGACACCGAGCTAG

FIG. 45

MLKKQSAGLVLWGAILFVAWNALLLLFFWTRPAPGRPPSVSALDGDPASLTREVDMQSSGELRTGGARPPPPLGASSQPRPGGDSSPVVDSGPGPA
SNLTSVPVPHTTALSLPACPEESPLLVGPMLIEFNMPVDLELVAKQNPNVKMGGRYAPRDCVSPHKVAIIIPFRNRQEHLKYWLYYLHPVLQRQQL
DYGIYVINQAGDTIFNRAKLLNVGFQEALKDYDYTCFVFSDVDLIPMNDHNAYRCFSQPRHISVAMDKFGFSLPYVQYFGGVSALSKQQFLTINGF
PNNYWGWGGEDDDIFNRLVFRGMSISRPNAVVGRCRMIRHSRDKKNEPNPQRFDRIAHTKETMLSDGLNSLTYQVLDVQRYPLYTQITVDIGTPS

FIG. 46

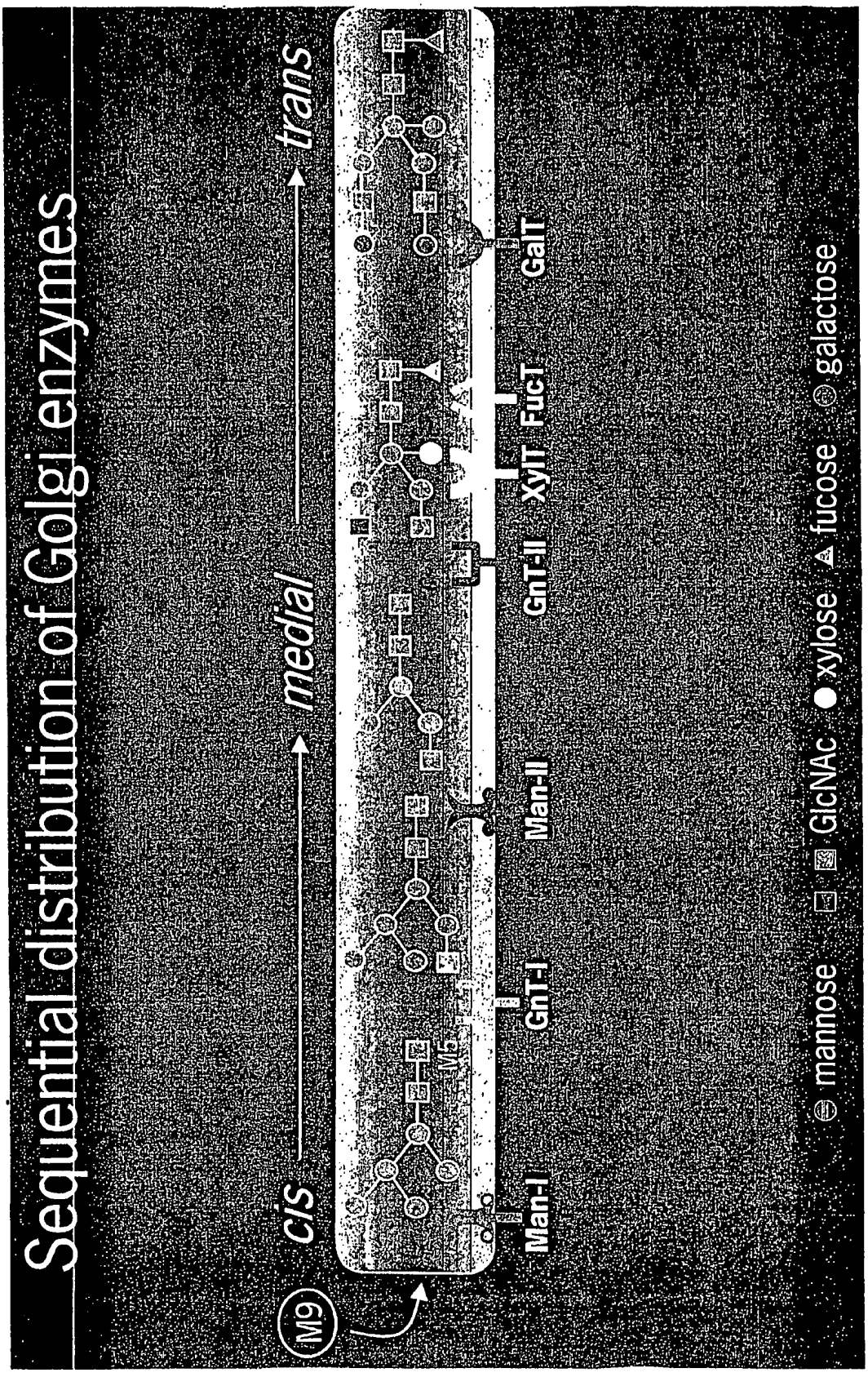
Sequential distribution of Golgi enzymes
cis
medial
trans
M9
M5
Man-I
GnT-I
Man-II
GnT-II
XylT
FucT
GalT
mannose
GlcNAc
xylose
fucose
galactose

FIG. 47

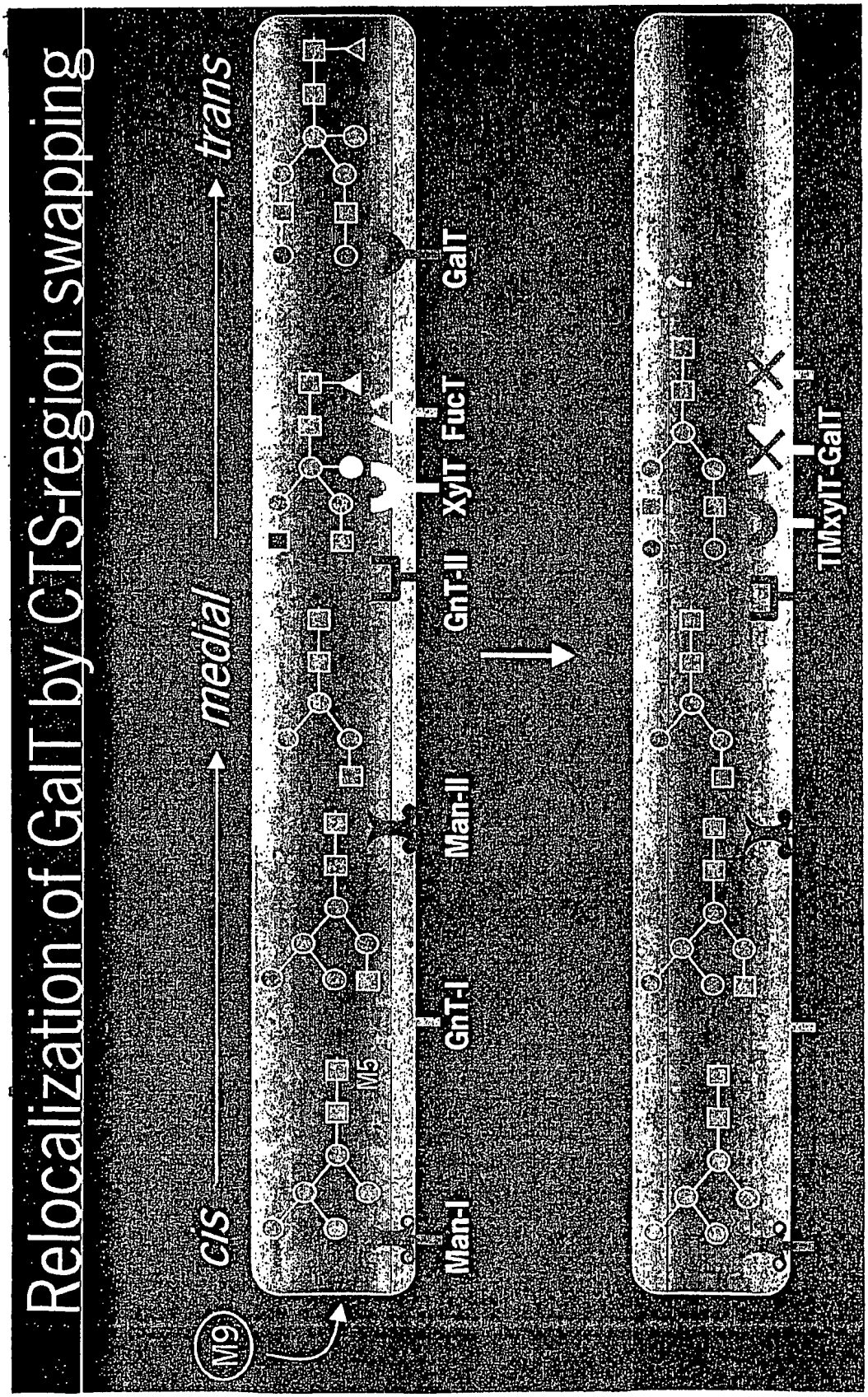
Relocalization of GalT by CTS-region swapping
cis
medial
trans
M9
M5
Man-I
GnT-I
Man-II
GnT-II
XylT
FucT
GalT
TMxylT-GalT

FIG. 48

SEQUENCE LISTING

<110> PLANT RESEARCH INTERNATIONAL BV
BAKKER, Hendrikus A.C.
FLORACK, Dionisius E.A.
BOSCH, Hendrik J.
ROWENDAL, Gerard J.A.

<120> Optimizing glycan processing in plants

<130> 62861A - PD33486WO

<150> US-60/365,735
<151> 2002-03-19

<160> 59

<170> PatentIn version 3.2

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<211> 1197
<212> DNA
<213> Homo sapiens

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tacctggctg gccgcgacct gagccgcctg ccccaactgg tcggagtctc cacaccgctg 180
cagggcggct cgaacagtgc cgccgccatc gggcagtcct ccggggagct ccggaccgga 240
ggggcccggc cgccgcctcc tctaggcgcc tcctcccagc cgcgcccggg tggcgactcc 300
agcccagtcg tggattctgg ccctggcccc gctagcaact tgacctcggt cccagtgccc 360
cacaccaccg cactgtcgct gcccgcctgc cctgaggagt ccccgctgct tgtgggcccc 420
atgctgattg agtttaacat gcctgtggac ctggagctcg tggcaaagca gaacccaaat 480
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gtcctgcagc gccagcagct ggactatggc atctatgtta tcaaccaggc gggagacact 660
atattcaatc gtgctaagct cctcaatgtt ggctttcaag aagccttgaa ggactatgac 720
tacacctgct ttgtgtttag tgacgtggac ctcattccaa tgaatgacca taatgcgtac 780
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ccttatgttc agtattttgg aggtgtctct gctctaagta aacaacagtt tctaaccatc 900
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ttagttttta gaggcatgtc tatatctcgc ccaaatgctg tggtcgggag gtgtcgcatg 1020
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cacacaaagg agacaatgct ctctgatggt ttgaactcac tcacctacca ggtgctggat 1140
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<212> PRT
<213> Homo sapiens

<400> 2

Met Arg Leu Arg Glu Pro Leu Leu Ser Gly Ser Ala Ala Met Pro Gly
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Ala Ser Leu Gln Arg Ala Cys Arg Leu Leu Val Ala Val Cys Ala Leu
20 25 30

His Leu Gly Val Thr Leu Val Tyr Tyr Leu Ala Gly Arg Asp Leu Ser
35 40 45

Arg Leu Pro Gln Leu Val Gly Val Ser Thr Pro Leu Gln Gly Gly Ser
50 55 60

Asn Ser Ala Ala Ala Ile Gly Gln Ser Ser Gly Glu Leu Arg Thr Gly

65 70 75 80

Gly Ala Arg Pro Pro Pro Pro Leu Gly Ala Ser Ser Gln Pro Arg Pro
85 90 95

Gly Gly Asp Ser Ser Pro Val Val Asp Ser Gly Pro Gly Pro Ala Ser
100 105 110

Asn Leu Thr Ser Val Pro Val Pro His Thr Thr Ala Leu Ser Leu Pro
115 120 125

Ala Cys Pro Glu Glu Ser Pro Leu Leu Val Gly Pro Met Leu Ile Glu
130 135 140

Phe Asn Met Pro Val Asp Leu Glu Leu Val Ala Lys Gln Asn Pro Asn
145 150 155 160

Val Lys Met Gly Gly Arg Tyr Ala Pro Arg Asp Cys Val Ser Pro His
165 170 175

Lys Val Ala Ile Ile Ile Pro Phe Arg Asn Arg Gln Glu His Leu Lys
180 185 190

Tyr Trp Leu Tyr Tyr Leu His Pro Val Leu Gln Arg Gln Gln Leu Asp
195 200 205

Tyr Gly Ile Tyr Val Ile Asn Gln Ala Gly Asp Thr Ile Phe Asn Arg
210 215 220

Ala Lys Leu Leu Asn Val Gly Phe Gln Glu Ala Leu Lys Asp Tyr Asp
225 230 235 240

Tyr Thr Cys Phe Val Phe Ser Asp Val Asp Leu Ile Pro Met Asn Asp
245 250 255

His Asn Ala Tyr Arg Cys Phe Ser Gln Pro Arg His Ile Ser Val Ala
260 265 270

Met Asp Lys Phe Gly Phe Ser Leu Pro Tyr Val Gln Tyr Phe Gly Gly
275 280 285

Val Ser Ala Leu Ser Lys Gln Gln Phe Leu Thr Ile Asn Gly Phe Pro
290 295 300

Asn Asn Tyr Trp Gly Trp Gly Gly Glu Asp Asp Asp Ile Phe Asn Arg
305 310 315 320

Leu Val Phe Arg Gly Met Ser Ile Ser Arg Pro Asn Ala Val Val Gly
325 330 335

Arg Cys Arg Met Ile Arg His Ser Arg Asp Lys Lys Asn Glu Pro Asn
340 345 350

Pro Gln Arg Phe Asp Arg Ile Ala His Thr Lys Glu Thr Met Leu Ser
355 360 365

Asp Gly Leu Asn Ser Leu Thr Tyr Gln Val Leu Asp Val Gln Arg Tyr
370 375 380

Pro Leu Tyr Thr Gln Ile Thr Val Asp Ile Gly Thr Pro Ser
385 390 395

<210> 3
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cctcctcata tataccacgt ttcagtgaat aaccaatcgg cgatcgggca gtcctccggg 180
gagctccgga ccggaggggc ccggccgccg cctcctctag gcgcctcctc ccagccgcgc 240
ccgggtggcg actccagccc agtcgtggat tctggccctg gccccgctag caacttgacc 300
tcggtcccag tgccccacac caccgcactg tcgctgcccg cctgccctga ggagtccccg 360
ctgcttgtgg gccccatgct gattgagttt aacatgcctg tggacctgga gctcgtggca 420
aagcagaacc caaatgtgaa gatgggcggc cgctatgccc ccagggactg cgtctctcct 480
cacaaggtgg ccatcatcat tccattccgc aaccggcagg agcacctcaa gtactggcta 540
tattatttgc acccagtcct gcagcgccag cagctggact atggcatcta tgttatcaac 600
caggcgggag acactatatt caatcgtgct aagctcctca atgttggctt tcaagaagcc 660
ttgaaggact atgactacac ctgctttgtg tttagtgacg tggacctcat tccaatgaat 720
gaccataatg cgtacaggtg tttttcacag ccacggcaca tttccgttgc aatggataag 780
tttggattca gcctacctta tgttcagtat tttggaggtg tctctgctct aagtaaacaa 840
cagtttctaa ccatcaatgg atttcctaat aattattggg gctggggagg agaagatgat 900
gacattttta acagattagt ttttagaggc atgtctatat ctcgcccaaa tgctgtggtc 960
gggaggtgtc gcatgatccg ccactcaaga gacaagaaaa atgaacccaa tcctcagagg 1020
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acaccgagct ag 1152

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<211> 383
<212> PRT
<213> hybrid

<400> 4

Met Ser Lys Arg Asn Pro Lys Ile Leu Lys Ile Phe Leu Tyr Met Leu
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Leu Leu Asn Ser Leu Phe Leu Ile Ile Tyr Phe Val Phe His Ser Ser
20 25 30

Ser Phe Ser Pro Glu Gln Ser Gln Pro Pro His Ile Tyr His Val Ser
35 40 45

Val Asn Asn Gln Ser Ala Ile Gly Gln Ser Ser Gly Glu Leu Arg Thr
50 55 60

Gly Gly Ala Arg Pro Pro Pro Pro Leu Gly Ala Ser Ser Gln Pro Arg
65 70 75 80

Pro Gly Gly Asp Ser Ser Pro Val Val Asp Ser Gly Pro Gly Pro Ala
85 90 95

Ser Asn Leu Thr Ser Val Pro Val Pro His Thr Thr Ala Leu Ser Leu
100 105 110

Pro Ala Cys Pro Glu Glu Ser Pro Leu Leu Val Gly Pro Met Leu Ile
115 120 125

Glu Phe Asn Met Pro Val Asp Leu Glu Leu Val Ala Lys Gln Asn Pro
130 135 140

Asn Val Lys Met Gly Gly Arg Tyr Ala Pro Arg Asp Cys Val Ser Pro
145 150 155 160

His Lys Val Ala Ile Ile Ile Pro Phe Arg Asn Arg Gln Glu His Leu
165 170 175

Lys Tyr Trp Leu Tyr Tyr Leu His Pro Val Leu Gln Arg Gln Gln Leu
180 185 190

Asp Tyr Gly Ile Tyr Val Ile Asn Gln Ala Gly Asp Thr Ile Phe Asn
195 200 205

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Arg Ala Lys Leu Leu Asn Val Gly Phe Gln Glu Ala Leu Lys Asp Tyr
    210                 215                 220

Asp Tyr Thr Cys Phe Val Phe Ser Asp Val Asp Leu Ile Pro Met Asn
225                 230                 235                 240

Asp His Asn Ala Tyr Arg Cys Phe Ser Gln Pro Arg His Ile Ser Val
                245                 250                 255

Ala Met Asp Lys Phe Gly Phe Ser Leu Pro Tyr Val Gln Tyr Phe Gly
            260                 265                 270

Gly Val Ser Ala Leu Ser Lys Gln Gln Phe Leu Thr Ile Asn Gly Phe
        275                 280                 285

Pro Asn Asn Tyr Trp Gly Trp Gly Gly Glu Asp Asp Asp Ile Phe Asn
    290                 295                 300

Arg Leu Val Phe Arg Gly Met Ser Ile Ser Arg Pro Asn Ala Val Val
305                 310                 315                 320

Gly Arg Cys Arg Met Ile Arg His Ser Arg Asp Lys Lys Asn Glu Pro
                325                 330                 335

Asn Pro Gln Arg Phe Asp Arg Ile Ala His Thr Lys Glu Thr Met Leu
            340                 345                 350

Ser Asp Gly Leu Asn Ser Leu Thr Tyr Gln Val Leu Asp Val Gln Arg
        355                 360                 365

Tyr Pro Leu Tyr Thr Gln Ile Thr Val Asp Ile Gly Thr Pro Ser
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<211> 1642
<212> DNA
<213> Homo sapiens

<400> 5

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ccctcagccc taacctggtg tccagctttt tctggaacaa tgccccggtc acgccccagg    180
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tgctgcagcc gctgccgccc agcaaggcgg ccgaggagct ccaccgggtg gacttggtgc    300
tgcccgagga caccaccgag tatttcgtgc gcaccaaggc cggcggcgtc tgcttcaaac    360
ccggcaccaa gatgctggag aggccgcccc cgggacggcc ggaggagaag cctgaggggg    420
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tgctggacgt gcgcttccac gagctgggcg acgtggtgga cgcctttgtg gtgtgcgagt    720
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gcggccggca ggacggctgg atcgccgacg actacctgcg caccttcctc acccaggacg    900
gcgtctcgcg gctgcgcaac ctgcggcccg acgacgtctt catcattgac gatgcggacg    960
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aggtggtgtc aggctgcacg gtggacatgc tgcaggcagt gtatgggctg gacggcatcc   1140
gcctgcgccg ccgccagtac tacaccatgc ccaacttcag acagtatgag aaccgcaccg   1200
gccacatcct ggtgcagtgg tcgctgggca gccccctgca cttcgccggc tggcactgct   1260
cctggtgctt cacgcccgag ggcatctact tcaagctcgt gtccgcccag aatggcgact   1320
tcccacgctg gggtgactac gaggacaagc gggacctgaa ctacatccgc ggcctgatcc   1380
gcaccggggg ctggttcgac ggcacgcagc aggagtaccc gcctgcagac cccagcgagc   1440
acatgtatgc gcccaagtac ctgctgaaga actacgaccg gttccactac ctgctggaca   1500
acccctacca ggagcccagg agcacggcgg cgggcgggtg gcgccacagg ggtcccgagg   1560
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<212> PRT
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<400> 6

Met Val Met Arg Arg Tyr Lys Leu Phe Leu Met Phe Cys Met Ala Gly
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Leu Cys Leu Ile Ser Phe Leu His Phe Phe Lys Thr Leu Ser Tyr Val
20 25 30

Thr Phe Pro Arg Glu Leu Ala Ser Leu Ser Pro Asn Leu Val Ser Ser
35 40 45

Phe Phe Trp Asn Asn Ala Pro Val Thr Pro Gln Ala Ser Pro Glu Pro
50 55 60

Gly Gly Pro Asp Leu Leu Arg Thr Pro Leu Tyr Ser His Ser Pro Leu
65 70 75 80

Leu Gln Pro Leu Pro Pro Ser Lys Ala Ala Glu Glu Leu His Arg Val
85 90 95

Asp Leu Val Leu Pro Glu Asp Thr Thr Glu Tyr Phe Val Arg Thr Lys
100 105 110

Ala Gly Gly Val Cys Phe Lys Pro Gly Thr Lys Met Leu Glu Arg Pro
115 120 125

Pro Pro Gly Arg Pro Glu Glu Lys Pro Glu Gly Ala Asn Gly Ser Ser
130 135 140

Ala Arg Arg Pro Pro Arg Tyr Leu Leu Ser Ala Arg Glu Arg Thr Gly
145 150 155 160

Gly Arg Gly Ala Arg Arg Lys Trp Val Glu Cys Val Cys Leu Pro Gly
165 170 175

Trp His Gly Pro Ser Cys Gly Val Pro Thr Val Val Gln Tyr Ser Asn
180 185 190

Leu Pro Thr Lys Glu Arg Leu Val Pro Arg Glu Val Pro Arg Arg Val
195 200 205

Ile Asn Ala Ile Asn Val Asn His Glu Phe Asp Leu Leu Asp Val Arg
210 215 220

Phe His Glu Leu Gly Asp Val Val Asp Ala Phe Val Val Cys Glu Ser
225 230 235 240

Asn Phe Thr Ala Tyr Gly Glu Pro Arg Pro Leu Lys Phe Arg Glu Met
245 250 255

Leu Thr Asn Gly Thr Phe Glu Tyr Ile Arg His Lys Val Leu Tyr Val
260 265 270

Phe Leu Asp His Phe Pro Pro Gly Gly Arg Gln Asp Gly Trp Ile Ala
275 280 285

Asp Asp Tyr Leu Arg Thr Phe Leu Thr Gln Asp Gly Val Ser Arg Leu
290 295 300

Arg Asn Leu Arg Pro Asp Asp Val Phe Ile Ile Asp Asp Ala Asp Glu

305 310 315 320

Ile Pro Ala Arg Asp Gly Val Leu Phe Leu Lys Leu Tyr Asp Gly Trp
325 330 335

Thr Glu Pro Phe Ala Phe His Met Arg Lys Ser Leu Tyr Gly Phe Phe
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Trp Lys Gln Pro Gly Thr Leu Glu Val Val Ser Gly Cys Thr Val Asp
355 360 365

Met Leu Gln Ala Val Tyr Gly Leu Asp Gly Ile Arg Leu Arg Arg Arg
370 375 380

Gln Tyr Tyr Thr Met Pro Asn Phe Arg Gln Tyr Glu Asn Arg Thr Gly
385 390 395 400

His Ile Leu Val Gln Trp Ser Leu Gly Ser Pro Leu His Phe Ala Gly
405 410 415

Trp His Cys Ser Trp Cys Phe Thr Pro Glu Gly Ile Tyr Phe Lys Leu
420 425 430

Val Ser Ala Gln Asn Gly Asp Phe Pro Arg Trp Gly Asp Tyr Glu Asp
435 440 445

Lys Arg Asp Leu Asn Tyr Ile Arg Gly Leu Ile Arg Thr Gly Gly Trp
450 455 460

Phe Asp Gly Thr Gln Gln Glu Tyr Pro Pro Ala Asp Pro Ser Glu His
465 470 475 480

Met Tyr Ala Pro Lys Tyr Leu Leu Lys Asn Tyr Asp Arg Phe His Tyr
485 490 495

Leu Leu Asp Asn Pro Tyr Gln Glu Pro Arg Ser Thr Ala Ala Gly Gly
500 505 510

Trp Arg His Arg Gly Pro Glu Gly Arg Pro Pro Ala Arg Gly Lys Leu
515 520 525

Asp Glu Ala Glu Val Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asn
530 535 540

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<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 7

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<210> 8
<211> 31
<212> PRT
<213> Homo sapiens

<400> 8

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Glu Gly Arg Pro Pro Ala Arg Gly Lys Leu Asp Glu Ala Glu Val
20 25 30

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<211> 1614
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gctgcgtacc ccactctact cccactcgcc cctgctgcag ccgctgccgc ccagcaaggc 240
ggccgaggag ctccaccggg tggacttggt gctgcccgag gacaccaccg agtatttcgt 300
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cccgggacgg ccggaggaga agcctgaggg ggccaacggc tcctcggccc ggcggccacc 420
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gccgctcaag ttccgggaga tgctgaccaa tggcaccttc gagtacatcc gccacaaggt 780
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ggcgggcggg tggcgccaca ggggtcccga gggaaggccg cccgcccggg gcaaactgga 1560
cgaggcggaa gtcgaacaaa aactcatctc agaagaggat ctgaattagg atcc 1614

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<211> 535
<212> PRT
<213> hybrid

<400> 10

Met Ser Lys Arg Asn Pro Lys Ile Leu Lys Ile Phe Leu Tyr Met Leu
1 5 10 15

Leu Leu Asn Ser Leu Phe Leu Ile Ile Tyr Phe Val Phe His Ser Ser
20 25 30

Ser Phe Ser Pro Glu Gln Ser Gln Pro Pro His Ile Tyr His Val Ser
35 40 45

Val Asn Asn Gln Ser Ala His Gly Gly Pro Asp Leu Leu Arg Thr Pro
50 55 60

Leu Tyr Ser His Ser Pro Leu Leu Gln Pro Leu Pro Pro Ser Lys Ala
65 70 75 80

Ala Glu Glu Leu His Arg Val Asp Leu Val Leu Pro Glu Asp Thr Thr
85 90 95

Glu Tyr Phe Val Arg Thr Lys Ala Gly Gly Val Cys Phe Lys Pro Gly
100 105 110

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Thr Lys Met Leu Glu Arg Pro Pro Pro Gly Arg Pro Glu Glu Lys Pro
        115                 120                 125

Glu Gly Ala Asn Gly Ser Ser Ala Arg Arg Pro Pro Arg Tyr Leu Leu
    130                 135                 140

Ser Ala Arg Glu Arg Thr Gly Gly Arg Gly Ala Arg Arg Lys Trp Val
145                 150                 155                 160

Glu Cys Val Cys Leu Pro Gly Trp His Gly Pro Ser Cys Gly Val Pro
                165                 170                 175

Thr Val Val Gln Tyr Ser Asn Leu Pro Thr Lys Glu Arg Leu Val Pro
            180                 185                 190

Arg Glu Val Pro Arg Arg Val Ile Asn Ala Ile Asn Val Asn His Glu
        195                 200                 205

Phe Asp Leu Leu Asp Val Arg Phe His Glu Leu Gly Asp Val Val Asp
    210                 215                 220

Ala Phe Val Val Cys Glu Ser Asn Phe Thr Ala Tyr Gly Glu Pro Arg
225                 230                 235                 240

Pro Leu Lys Phe Arg Glu Met Leu Thr Asn Gly Thr Phe Glu Tyr Ile
                245                 250                 255

Arg His Lys Val Leu Tyr Val Phe Leu Asp His Phe Pro Pro Gly Gly
            260                 265                 270

Arg Gln Asp Gly Trp Ile Ala Asp Asp Tyr Leu Arg Thr Phe Leu Thr
        275                 280                 285

Gln Asp Gly Val Ser Arg Leu Arg Asn Leu Arg Pro Asp Asp Val Phe
    290                 295                 300

Ile Ile Asp Asp Ala Asp Glu Ile Pro Ala Arg Asp Gly Val Leu Phe
305                 310                 315                 320

Leu Lys Leu Tyr Asp Gly Trp Thr Glu Pro Phe Ala Phe His Met Arg
                325                 330                 335

Lys Ser Leu Tyr Gly Phe Phe Trp Lys Gln Pro Gly Thr Leu Glu Val
            340                 345                 350

Val Ser Gly Cys Thr Val Asp Met Leu Gln Ala Val Tyr Gly Leu Asp
        355                 360                 365

Gly Ile Arg Leu Arg Arg Arg Gln Tyr Tyr Thr Met Pro Asn Phe Arg
    370                 375                 380

Gln Tyr Glu Asn Arg Thr Gly His Ile Leu Val Gln Trp Ser Leu Gly
385                 390                 395                 400

Ser Pro Leu His Phe Ala Gly Trp His Cys Ser Trp Cys Phe Thr Pro
                405                 410                 415

Glu Gly Ile Tyr Phe Lys Leu Val Ser Ala Gln Asn Gly Asp Phe Pro
            420                 425                 430

Arg Trp Gly Asp Tyr Glu Asp Lys Arg Asp Leu Asn Tyr Ile Arg Gly
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Leu Lys Glu Ser Glu Ala Asp Ile Asp Thr Val Ala Ile Tyr Pro Thr
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Phe Asp Phe Gln Pro Ser Trp Leu Arg Thr Lys Glu Phe Trp Asp Lys
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Ser Phe Glu Asp Arg Tyr Glu Arg Ile His Asn Asp Thr Thr Arg Pro
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    130                 135                 140

Trp Thr Glu Ile Ser Phe Leu Asn Ala Trp Trp Glu Arg Ser His Pro
145                 150                 155                 160

Val Lys Gln Lys Ala Leu Lys Lys Leu Ile Lys Glu Gly Arg Leu Glu
                165                 170                 175

Ile Thr Thr Gly Gly Trp Val Met Pro Asp Glu Ala Cys Thr His Ile
            180                 185                 190

Tyr Ala Leu Ile Asp Gln Phe Ile Glu Gly His His Trp Val Lys Thr
        195                 200                 205

Asn Leu Gly Val Ile Pro Lys Thr Gly Trp Ser Ile Asp Pro Phe Gly
    210                 215                 220

His Gly Ala Thr Val Pro Tyr Leu Leu Asp Gln Ser Gly Leu Glu Gly
225                 230                 235                 240

Thr Ile Ile Gln Arg Ile His Tyr Ala Trp Lys Gln Trp Leu Ala Glu
                245                 250                 255

Arg Gln Ile Glu Glu Phe Tyr Trp Leu Ala Ser Trp Ala Thr Thr Lys
            260                 265                 270

Pro Ser Met Ile Val His Asn Gln Pro Phe Asp Ile Tyr Ser Ile Lys
        275                 280                 285

Ser Thr Cys Gly Pro His Pro Ser Ile Cys Leu Ser Phe Asp Phe Arg
    290                 295                 300

Lys Ile Pro Gly Glu Tyr Ser Glu Tyr Thr Ala Lys His Glu Asp Ile
305                 310                 315                 320

Thr Glu His Asn Leu His Ser Lys Ala Lys Thr Leu Ile Glu Glu Tyr
                325                 330                 335

Asp Arg Ile Gly Ser Leu Thr Pro His Asn Val Val Leu Val Pro Leu
            340                 345                 350

Gly Asp Asp Phe Arg Tyr Glu Tyr Ser Val Glu Phe Asp Ala Gln Tyr
        355                 360                 365

Val Asn Tyr Met Lys Met Phe Asn Tyr Ile Asn Ala His Lys Glu Ile
    370                 375                 380

Phe Asn Ala Asp Val Gln Phe Gly Thr Pro Leu Asp Tyr Phe Asn Ala
385                 390                 395                 400

Met Lys Glu Arg His Gln Asn Ile Pro Ser Leu Lys Gly Asp Phe Phe
                405                 410                 415

Val Tyr Ser Asp Ile Phe Ser Glu Gly Lys Pro Ala Tyr Trp Ser Gly
            420                 425                 430

Tyr Tyr Thr Thr Arg Pro Tyr Gln Lys Ile Leu Ala Arg Gln Phe Glu
        435                 440                 445

His Gln Leu Arg Ser Ala Glu Ile Leu Phe Thr Leu Val Ser Asn Tyr
    450                 455                 460

Ile Arg Gln Met Gly Arg Gln Gly Glu Phe Gly Ala Ser Glu Lys Lys
```

465 470 475 480

Leu Glu Lys Ser Tyr Glu Gln Leu Ile Tyr Ala Arg Arg Asn Leu Gly
485 490 495

Leu Phe Gln His His Asp Ala Ile Thr Gly Thr Ser Lys Ser Ser Val
500 505 510

Met Gln Asp Tyr Gly Thr Lys Leu Phe Thr Ser Leu Tyr His Cys Ile
515 520 525

Arg Leu Gln Glu Ala Ala Leu Thr Thr Ile Met Leu Pro Asp Gln Ser
530 535 540

Leu His Ser Gln Ser Ile Ile Gln Ser Glu Val Glu Trp Glu Thr Tyr
545 550 555 560

Gly Lys Pro Pro Lys Lys Leu Gln Val Ser Phe Ile Asp Lys Lys Lys
565 570 575

Val Ile Leu Phe Asn Pro Leu Ala Glu Thr Arg Thr Glu Val Val Thr
580 585 590

Val Arg Ser Asn Thr Ser Asn Ile Arg Val Tyr Asp Thr His Lys Arg
595 600 605

Lys His Val Leu Tyr Gln Ile Met Pro Ser Ile Thr Ile Gln Asp Asn
610 615 620

Gly Lys Ser Ile Val Ser Asp Thr Thr Phe Asp Ile Met Phe Val Ala
625 630 635 640

Thr Ile Pro Pro Leu Thr Ser Ile Ser Tyr Lys Leu Gln Glu His Thr
645 650 655

Asn Thr Ser His His Cys Val Ile Phe Cys Asn Asn Cys Glu Gln Tyr
660 665 670

Gln Lys Ser Asn Val Phe Gln Ile Lys Lys Met Met Pro Gly Asp Ile
675 680 685

Gln Leu Glu Asn Ala Val Leu Lys Leu Leu Val Asn Arg Asn Thr Gly
690 695 700

Phe Leu Arg Gln Val Tyr Arg Lys Asp Ile Arg Lys Arg Thr Val Val
705 710 715 720

Asp Val Gln Phe Gly Ala Tyr Gln Ser Ala Gln Arg His Ser Gly Ala
725 730 735

Tyr Leu Phe Met Pro His Tyr Asp Ser Pro Glu Lys Asn Val Leu His
740 745 750

Pro Tyr Thr Asn Gln Asn Asn Met Gln Asp Asp Asn Ile Ile Ile Val
755 760 765

Ser Gly Pro Ile Ser Thr Glu Ile Thr Thr Met Tyr Leu Pro Phe Leu
770 775 780

Val His Thr Ile Arg Ile Tyr Asn Val Pro Asp Pro Val Leu Ser Arg
785 790 795 800

Ala Ile Leu Leu Glu Thr Asp Val Asp Phe Glu Ala Pro Pro Lys Asn
805 810 815

Arg Glu Thr Glu Leu Phe Met Arg Leu Gln Thr Asp Ile Gln Asn Gly
820 825 830

```
Asp Ile Pro Glu Phe Tyr Thr Asp Gln Asn Gly Phe Gln Tyr Gln Lys
        835                 840                 845

Arg Val Lys Val Asn Lys Leu Gly Ile Glu Ala Asn Tyr Tyr Pro Ile
    850                 855                 860

Thr Thr Met Ala Cys Leu Gln Asp Glu Glu Thr Arg Leu Thr Leu Leu
865                 870                 875                 880

Thr Asn His Ala Gln Gly Ala Ala Ala Tyr Glu Pro Gly Arg Leu Glu
                885                 890                 895

Val Met Leu Asp Arg Arg Thr Leu Tyr Asp Asp Phe Arg Gly Ile Gly
            900                 905                 910

Glu Gly Val Val Asp Asn Lys Pro Thr Thr Phe Gln Asn Trp Ile Leu
        915                 920                 925

Ile Glu Ser Met Pro Gly Val Thr Arg Ala Lys Arg Asp Thr Ser Glu
    930                 935                 940

Pro Gly Phe Lys Phe Val Asn Glu Arg Arg Phe Gly Pro Gly Gln Lys
945                 950                 955                 960

Glu Ser Pro Tyr Gln Val Pro Ser Gln Thr Ala Asp Tyr Leu Ser Arg
                965                 970                 975

Met Phe Asn Tyr Pro Val Asn Val Tyr Leu Val Asp Thr Ser Glu Val
            980                 985                 990

Gly Glu Ile Glu Val Lys Pro Tyr  Gln Ser Phe Leu Gln  Ser Phe Pro
        995                 1000                1005

Pro Gly  Ile His Leu Val Thr  Leu Arg Thr Ile Thr  Asp Asp Val
    1010                1015                1020

Leu Glu  Leu Phe Pro Ser Asn  Glu Ser Tyr Met Val  Leu His Arg
    1025                1030                1035

Pro Gly  Tyr Ser Cys Ala Val  Gly Glu Lys Pro Val  Ala Lys Ser
    1040                1045                1050

Pro Lys  Phe Ser Ser Lys Thr  Arg Phe Asn Gly Leu  Asn Ile Gln
    1055                1060                1065

Asn Ile  Thr Ala Val Ser Leu  Thr Gly Leu Lys Ser  Leu Arg Pro
    1070                1075                1080

Leu Thr  Gly Leu Ser Asp Ile  His Leu Asn Ala Met  Glu Val Lys
    1085                1090                1095

Thr Tyr  Lys Ile Arg Phe Lys  Asp Glu Leu
    1100                1105
```

<210> 51
<211> 1068
<212> DNA
<213> hybrid

<400> 51
atgggcatca agatggagac acattctcag gtctttgtat acatgttgct gtggttgtct 60
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ctaggcgcct cctcccagcc gcgcccgggt ggcgactcca gcccagtcgt ggattctggc 180
cctggccccg ctagcaactt gacctcggtc ccagtgcccc acaccaccgc actgtcgctg 240
cccgcctgcc ctgaggagtc cccgctgctt gtgggcccca tgctgattga gtttaacatg 300
cctgtggacc tggagctcgt ggcaaagcag aacccaaatg tgaagatggg cggccgctat 360
gcccccaggg actgcgtctc tcctcacaag gtggccatca tcattccatt ccgcaaccgg 420

caggagcacc tcaagtactg gctatattat ttgcacccag tcctgcagcg ccagcagctg 480
gactatggca tctatgttat caaccaggcg ggagacacta tattcaatcg tgctaagctc 540
ctcaatgttg gctttcaaga agccttgaag gactatgact acacctgctt tgtgtttagt 600
gacgtggacc tcattccaat gaatgaccat aatgcgtaca ggtgtttttc acagccacgg 660
cacatttccg ttgcaatgga taagtttgga ttcagcctac cttatgttca gtattttgga 720
ggtgtctctg ctctaagtaa acaacagttt ctaaccatca atggatttcc taataattat 780
tggggctggg gaggagaaga tgatgacatt tttaacagat tagtttttag aggcatgtct 840
atatctcgcc caaatgctgt ggtcgggagg tgtcgcatga tccgccactc aagagacaag 900
aaaaatgaac ccaatcctca gaggtttgac cgaattgcac acacaaagga gacaatgctc 960
tctgatggtt tgaactcact cacctaccag gtgctggatg tacagagata cccattgtat 1020
acccaaatca cagtggacat cgggacaccg agcaaggacg agctttag 1068

<210> 52
<211> 355
<212> PRT
<213> hybrid

<400> 52

Met Gly Ile Lys Met Glu Thr His Ser Gln Val Phe Val Tyr Met Leu
1 5 10 15

Leu Trp Leu Ser Gly Val Asp Met Gln Ser Ser Gly Glu Leu Arg Thr
20 25 30

Gly Gly Ala Arg Pro Pro Pro Pro Leu Gly Ala Ser Ser Gln Pro Arg
35 40 45

Pro Gly Gly Asp Ser Ser Pro Val Val Asp Ser Gly Pro Gly Pro Ala
50 55 60

Ser Asn Leu Thr Ser Val Pro Val Pro His Thr Thr Ala Leu Ser Leu
65 70 75 80

Pro Ala Cys Pro Glu Glu Ser Pro Leu Leu Val Gly Pro Met Leu Ile
85 90 95

Glu Phe Asn Met Pro Val Asp Leu Glu Leu Val Ala Lys Gln Asn Pro
100 105 110

Asn Val Lys Met Gly Gly Arg Tyr Ala Pro Arg Asp Cys Val Ser Pro
115 120 125

His Lys Val Ala Ile Ile Ile Pro Phe Arg Asn Arg Gln Glu His Leu
130 135 140

Lys Tyr Trp Leu Tyr Tyr Leu His Pro Val Leu Gln Arg Gln Gln Leu
145 150 155 160

Asp Tyr Gly Ile Tyr Val Ile Asn Gln Ala Gly Asp Thr Ile Phe Asn
165 170 175

Arg Ala Lys Leu Leu Asn Val Gly Phe Gln Glu Ala Leu Lys Asp Tyr
180 185 190

Asp Tyr Thr Cys Phe Val Phe Ser Asp Val Asp Leu Ile Pro Met Asn
195 200 205

Asp His Asn Ala Tyr Arg Cys Phe Ser Gln Pro Arg His Ile Ser Val
210 215 220

Ala Met Asp Lys Phe Gly Phe Ser Leu Pro Tyr Val Gln Tyr Phe Gly
225 230 235 240

Gly Val Ser Ala Leu Ser Lys Gln Gln Phe Leu Thr Ile Asn Gly Phe
245 250 255

```
Pro Asn Asn Tyr Trp Gly Trp Gly Gly Glu Asp Asp Asp Ile Phe Asn
            260                 265                 270

Arg Leu Val Phe Arg Gly Met Ser Ile Ser Arg Pro Asn Ala Val Val
        275                 280                 285

Gly Arg Cys Arg Met Ile Arg His Ser Arg Asp Lys Lys Asn Glu Pro
    290                 295                 300

Asn Pro Gln Arg Phe Asp Arg Ile Ala His Thr Lys Glu Thr Met Leu
305                 310                 315                 320

Ser Asp Gly Leu Asn Ser Leu Thr Tyr Gln Val Leu Asp Val Gln Arg
                325                 330                 335

Tyr Pro Leu Tyr Thr Gln Ile Thr Val Asp Ile Gly Thr Pro Ser Lys
            340                 345                 350

Asp Glu Leu
        355
```

<210> 53
<211> 1119
<212> DNA
<213> hybrid

<400> 53

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atgggcatca agatggagac acattctcag gtctttgtat acatgttgct gtggttgtct     60
ggtgtcgaca tgggacagat gcctgtggct gctgtagtgg ttatggcctg cagtcgtgca    120
gactatcttg aaaggactgt taaatcagtt ttaacatatc aaactcccgt tgcttcaaaa    180
tatcctctat ttatatctca ggatggatct gatcaagctg tcaagagcaa gtcattgagc    240
tataatcaat taacatatat gcagcacttg gattttgaac cagtggtcac tgaaaggcct    300
ggcgaactga ctgcgtacta caagattgca cgtcactaca agtgggcact ggaccagttg    360
ttttacaaac acaaatttag tcgagtgatt atactagaag atgatatgga aattgctcca    420
gacttctttg attactttga ggctgcagct agtctcatgg atagggataa aaccattatg    480
gctgcttcat catggaatga taatggacag aagcagtttg tgcatgatcc ctatgcgcta    540
taccgatcag attttttttcc tggccttggg tggatgctca agagatcgac ttgggatgag    600
ttatcaccaa agtggccaaa ggcttactgg gatgattggc tgagactaaa ggaaaaccat    660
aaaggccgcc aattcattcg accggaagtc tgtagaacat acaattttgg tgaacatggg    720
tctagtttgg gacagttttt cagtcagtat ctggaaccta taaagctaaa cgatgtgacg    780
gttgactgga aagcaaagga cctgggatac ctgacagagg gaaactatac caagtacttt    840
tctggcttag tgagacaagc acgaccaatt caaggttctg accttgtctt aaaggctcaa    900
aacataaagg atgatgttcg tatccggtat aaagaccaag tagagtttga acgcattgca    960
ggggaatttg gtatatttga agaatggaag gatggtgtgc ctcgaacagc atataaagga   1020
gtagtggtgt ttcgaatcca gacaacaaga cgtgtattcc tggttgggcc agattctgta   1080
atgcagcttg gaattcgaaa ttccaaggac gagctttga                          1119
```

<210> 54
<211> 372
<212> PRT
<213> hybrid

<400> 54

```
Met Gly Ile Lys Met Glu Thr His Ser Gln Val Phe Val Tyr Met Leu
1               5                   10                  15

Leu Trp Leu Ser Gly Val Asp Met Gly Gln Met Pro Val Ala Ala Val
            20                  25                  30

Val Val Met Ala Cys Ser Arg Ala Asp Tyr Leu Glu Arg Thr Val Lys
        35                  40                  45

Ser Val Leu Thr Tyr Gln Thr Pro Val Ala Ser Lys Tyr Pro Leu Phe
    50                  55                  60
```

Ile Ser Gln Asp Gly Ser Asp Gln Ala Val Lys Ser Lys Ser Leu Ser
65 70 75 80

Tyr Asn Gln Leu Thr Tyr Met Gln His Leu Asp Phe Glu Pro Val Val
85 90 95

Thr Glu Arg Pro Gly Glu Leu Thr Ala Tyr Tyr Lys Ile Ala Arg His
100 105 110

Tyr Lys Trp Ala Leu Asp Gln Leu Phe Tyr Lys His Lys Phe Ser Arg
115 120 125

Val Ile Ile Leu Glu Asp Asp Met Glu Ile Ala Pro Asp Phe Phe Asp
130 135 140

Tyr Phe Glu Ala Ala Ala Ser Leu Met Asp Arg Asp Lys Thr Ile Met
145 150 155 160

Ala Ala Ser Ser Trp Asn Asp Asn Gly Gln Lys Gln Phe Val His Asp
165 170 175

Pro Tyr Ala Leu Tyr Arg Ser Asp Phe Phe Pro Gly Leu Gly Trp Met
180 185 190

Leu Lys Arg Ser Thr Trp Asp Glu Leu Ser Pro Lys Trp Pro Lys Ala
195 200 205

Tyr Trp Asp Asp Trp Leu Arg Leu Lys Glu Asn His Lys Gly Arg Gln
210 215 220

Phe Ile Arg Pro Glu Val Cys Arg Thr Tyr Asn Phe Gly Glu His Gly
225 230 235 240

Ser Ser Leu Gly Gln Phe Phe Ser Gln Tyr Leu Glu Pro Ile Lys Leu
245 250 255

Asn Asp Val Thr Val Asp Trp Lys Ala Lys Asp Leu Gly Tyr Leu Thr
260 265 270

Glu Gly Asn Tyr Thr Lys Tyr Phe Ser Gly Leu Val Arg Gln Ala Arg
275 280 285

Pro Ile Gln Gly Ser Asp Leu Val Leu Lys Ala Gln Asn Ile Lys Asp
290 295 300

Asp Val Arg Ile Arg Tyr Lys Asp Gln Val Glu Phe Glu Arg Ile Ala
305 310 315 320

Gly Glu Phe Gly Ile Phe Glu Glu Trp Lys Asp Gly Val Pro Arg Thr
325 330 335

Ala Tyr Lys Gly Val Val Val Phe Arg Ile Gln Thr Thr Arg Arg Val
340 345 350

Phe Leu Val Gly Pro Asp Ser Val Met Gln Leu Gly Ile Arg Asn Ser
355 360 365

Lys Asp Glu Leu
370

<210> 55
<211> 1158
<212> DNA
<213> hybrid

<400> 55
atgggcatca agatggagac acattctcag gtctttgtat acatgttgct gtggttgtct 60

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ggtgtcgaca tggctctaag gttgcataga aggaaccatt tttcgcctag aaatacggat    120
ctgttcccgg atttggcaaa agatcgtgtg gttatcgtct tgtatgtgca taatcgggct    180
cagtattttc gagtcacagt ggaaagtttg tcgaaggtta aaggtataag tgagacattg    240
ttgattgtta gtcatgatgg ttactttgaa gagatgaata ggattgtgga gagtattaag    300
ttttgtcaag tgaaacagat tttctcgcct tattcgcctc atatatatcg tactagcttc    360
ccgggtgtga ccctgaatga ttgtaagaac aagggtgatg aggcaaaggg gcattgtgaa    420
ggtaatcctg atcagtatgg gaatcatcgg tctccgaaga ttgtatcttt gaagcatcac    480
tggtggtgga tgatgaacac tgtatgggat gggttggaag agactaaagg acatgagggg    540
catatccttt tcattgaaga agatcatttt ctgtttccta atgcctatcg taacatacag    600
actcttacga ggctgaaacc cgcaaagtgt cctgactgtt ttgctgctaa tttagcaccg    660
tctgatgtga agtcaagagg agaagggctt gaaagtttgg ttgcagagag aatgggaaat    720
gttgggtatt cttttaatag aagtgtgtgg gagaatattc atcagaaggc aagagagttt    780
tgtttctttg atgattacaa ctgggatata acgatgtggg caacggtttt cccgtcgttt    840
ggttccccgg tgtacacatt gcgagggcct aggactagtg cggtacactt tggaaaatgt    900
gggttgcatc aaggtagagg agatgagggt gattgcatcg ataatggggt cgtaaacata    960
gaagttaagg aaacagataa agttgtgaac ataaaagaag gatggggagt tcgggtgtat   1020
aagcatcaag cgggttataa agccggtttc gaaggttggg gaggttgggg cgatgatagg   1080
gaccgacatt tatgtttgga ttttgccact atgtatcgtt acagcagtag cagtgcatct   1140
ccaaaggacg agctttga                                                 1158
```

<210> 56
<211> 385
<212> PRT
<213> hybrid

<400> 56

```
Met Gly Ile Lys Met Glu Thr His Ser Gln Val Phe Val Tyr Met Leu
1               5                  10                  15

Leu Trp Leu Ser Gly Val Asp Met Ala Leu Arg Leu His Arg Arg Asn
            20                  25                  30

His Phe Ser Pro Arg Asn Thr Asp Leu Phe Pro Asp Leu Ala Lys Asp
        35                  40                  45

Arg Val Val Ile Val Leu Tyr Val His Asn Arg Ala Gln Tyr Phe Arg
    50                  55                  60

Val Thr Val Glu Ser Leu Ser Lys Val Lys Gly Ile Ser Glu Thr Leu
65                  70                  75                  80

Leu Ile Val Ser His Asp Gly Tyr Phe Glu Glu Met Asn Arg Ile Val
                85                  90                  95

Glu Ser Ile Lys Phe Cys Gln Val Lys Gln Ile Phe Ser Pro Tyr Ser
            100                 105                 110

Pro His Ile Tyr Arg Thr Ser Phe Pro Gly Val Thr Leu Asn Asp Cys
        115                 120                 125

Lys Asn Lys Gly Asp Glu Ala Lys Gly His Cys Glu Gly Asn Pro Asp
    130                 135                 140

Gln Tyr Gly Asn His Arg Ser Pro Lys Ile Val Ser Leu Lys His His
145                 150                 155                 160

Trp Trp Trp Met Met Asn Thr Val Trp Asp Gly Leu Glu Glu Thr Lys
                165                 170                 175

Gly His Glu Gly His Ile Leu Phe Ile Glu Glu Asp His Phe Leu Phe
            180                 185                 190

Pro Asn Ala Tyr Arg Asn Ile Gln Thr Leu Thr Arg Leu Lys Pro Ala
        195                 200                 205

Lys Cys Pro Asp Cys Phe Ala Ala Asn Leu Ala Pro Ser Asp Val Lys
```

210 215 220

Ser Arg Gly Glu Gly Leu Glu Ser Leu Val Ala Glu Arg Met Gly Asn
225 230 235 240

Val Gly Tyr Ser Phe Asn Arg Ser Val Trp Glu Asn Ile His Gln Lys
245 250 255

Ala Arg Glu Phe Cys Phe Phe Asp Asp Tyr Asn Trp Asp Ile Thr Met
260 265 270

Trp Ala Thr Val Phe Pro Ser Phe Gly Ser Pro Val Tyr Thr Leu Arg
275 280 285

Gly Pro Arg Thr Ser Ala Val His Phe Gly Lys Cys Gly Leu His Gln
290 295 300

Gly Arg Gly Asp Glu Gly Asp Cys Ile Asp Asn Gly Val Val Asn Ile
305 310 315 320

Glu Val Lys Glu Thr Asp Lys Val Val Asn Ile Lys Glu Gly Trp Gly
325 330 335

Val Arg Val Tyr Lys His Gln Ala Gly Tyr Lys Ala Gly Phe Glu Gly
340 345 350

Trp Gly Gly Trp Gly Asp Asp Arg Asp Arg His Leu Cys Leu Asp Phe
355 360 365

Ala Thr Met Tyr Arg Tyr Ser Ser Ser Ser Ala Ser Pro Lys Asp Glu
370 375 380

Leu
385

<210> 57
<211> 1152
<212> DNA
<213> Homo sapiens

<400> 57
atgctgaaga agcagtctgc agggcttgtg ctgtggggcg ctatcctctt tgtggcctgg 60
aatgccctgc tgctcctctt cttctggacg cgcccagcac ctggcaggcc accctcagtc 120
agcgctctcg atggcgaccc cgccagcctc acccgggaag tcgacatgca gtcctccggg 180
gagctccgga ccggaggggc ccggccgccg cctcctctag gcgcctcctc ccagccgcgc 240
ccgggtggcg actccagccc agtcgtggat tctggccctg gccccgctag caacttgacc 300
tcggtcccag tgccccacac caccgcactg tcgctgcccg cctgccctga ggagtccccg 360
ctgcttgtgg gccccatgct gattgagttt aacatgcctg tggacctgga gctcgtggca 420
aagcagaacc caaatgtgaa gatgggcggc cgctatgccc ccagggactg cgtctctcct 480
cacaaggtgg ccatcatcat tccattccgc aaccggcagg agcacctcaa gtactggcta 540
tattatttgc acccagtcct gcagcgccag cagctggact atggcatcta tgttatcaac 600
caggcgggag acactatatt caatcgtgct aagctcctca atgttggctt tcaagaagcc 660
ttgaaggact atgactacac ctgctttgtg tttagtgacg tggacctcat tccaatgaat 720
gaccataatg cgtacaggtg tttttcacag ccacggcaca tttccgttgc aatggataag 780
tttggattca gcctacctta tgttcagtat tttggaggtg tctctgctct aagtaaacaa 840
cagtttctaa ccatcaatgg atttcctaat aattattggg gctggggagg agaagatgat 900
gacattttta acagattagt ttttagaggc atgtctatat ctcgcccaaa tgctgtggtc 960
gggaggtgtc gcatgatccg ccactcaaga gacaagaaaa atgaacccaa tcctcagagg 1020
tttgaccgaa ttgcacacac aaaggagaca atgctctctg atggtttgaa ctcactcacc 1080
taccaggtgc tggatgtaca gagataccca ttgtataccc aaatcacagt ggacatcggg 1140
acaccgagct ag 1152

<210> 58
<211> 383
<212> PRT
<213> Homo sapiens

<400> 58

```
Met Leu Lys Lys Gln Ser Ala Gly Leu Val Leu Trp Gly Ala Ile Leu
1               5                  10                  15

Phe Val Ala Trp Asn Ala Leu Leu Leu Leu Phe Phe Trp Thr Arg Pro
            20                  25                  30

Ala Pro Gly Arg Pro Pro Ser Val Ser Ala Leu Asp Gly Asp Pro Ala
        35                  40                  45

Ser Leu Thr Arg Glu Val Asp Met Gln Ser Ser Gly Glu Leu Arg Thr
    50                  55                  60

Gly Gly Ala Arg Pro Pro Pro Pro Leu Gly Ala Ser Ser Gln Pro Arg
65                  70                  75                  80

Pro Gly Gly Asp Ser Ser Pro Val Val Asp Ser Gly Pro Gly Pro Ala
                85                  90                  95

Ser Asn Leu Thr Ser Val Pro Val Pro His Thr Thr Ala Leu Ser Leu
            100                 105                 110

Pro Ala Cys Pro Glu Glu Ser Pro Leu Leu Val Gly Pro Met Leu Ile
        115                 120                 125

Glu Phe Asn Met Pro Val Asp Leu Glu Leu Val Ala Lys Gln Asn Pro
    130                 135                 140

Asn Val Lys Met Gly Gly Arg Tyr Ala Pro Arg Asp Cys Val Ser Pro
145                 150                 155                 160

His Lys Val Ala Ile Ile Ile Pro Phe Arg Asn Arg Gln Glu His Leu
                165                 170                 175

Lys Tyr Trp Leu Tyr Tyr Leu His Pro Val Leu Gln Arg Gln Gln Leu
            180                 185                 190

Asp Tyr Gly Ile Tyr Val Ile Asn Gln Ala Gly Asp Thr Ile Phe Asn
        195                 200                 205

Arg Ala Lys Leu Leu Asn Val Gly Phe Gln Glu Ala Leu Lys Asp Tyr
    210                 215                 220

Asp Tyr Thr Cys Phe Val Phe Ser Asp Val Asp Leu Ile Pro Met Asn
225                 230                 235                 240

Asp His Asn Ala Tyr Arg Cys Phe Ser Gln Pro Arg His Ile Ser Val
                245                 250                 255

Ala Met Asp Lys Phe Gly Phe Ser Leu Pro Tyr Val Gln Tyr Phe Gly
            260                 265                 270

Gly Val Ser Ala Leu Ser Lys Gln Gln Phe Leu Thr Ile Asn Gly Phe
        275                 280                 285

Pro Asn Asn Tyr Trp Gly Trp Gly Gly Glu Asp Asp Asp Ile Phe Asn
    290                 295                 300

Arg Leu Val Phe Arg Gly Met Ser Ile Ser Arg Pro Asn Ala Val Val
305                 310                 315                 320

Gly Arg Cys Arg Met Ile Arg His Ser Arg Asp Lys Lys Asn Glu Pro
                325                 330                 335

Asn Pro Gln Arg Phe Asp Arg Ile Ala His Thr Lys Glu Thr Met Leu
            340                 345                 350
```

Ser Asp Gly Leu Asn Ser Leu Thr Tyr Gln Val Leu Asp Val Gln Arg
355 360 365

Tyr Pro Leu Tyr Thr Gln Ile Thr Val Asp Ile Gly Thr Pro Ser
370 375 380

<210> 59
<211> 400
<212> PRT
<213> Homo sapiens

<400> 59

Met Arg Leu Arg Glu Pro Leu Leu Ser Gly Ala Ala Met Pro Gly Ala
1 5 10 15

Ser Leu Gln Arg Ala Cys Arg Leu Leu Val Ala Val Cys Ala Leu His
20 25 30

Leu Gly Val Thr Leu Val Tyr Tyr Leu Ala Gly Arg Asp Leu Ser Arg
35 40 45

Leu Pro Gln Leu Val Gly Val Ser Thr Pro Leu Gln Gly Gly Ser Asn
50 55 60

Ser Ala Ala Ala Ile Gly Gln Ser Ser Gly Glu Leu Arg Thr Gly Gly
65 70 75 80

Ala Arg Pro Pro Pro Pro Leu Gly Ala Ser Ser Gln Pro Arg Pro Gly
85 90 95

Gly Asp Ser Ser Pro Val Val Asp Ser Gly Pro Gly Pro Ala Ser Asn
100 105 110

Leu Thr Ser Val Pro Val Pro His Thr Thr Ala Leu Ser Leu Pro Ala
115 120 125

Cys Pro Glu Glu Ser Pro Leu Leu Val Gly Pro Met Leu Ile Glu Phe
130 135 140

Asn Met Pro Val Asp Leu Glu Leu Val Ala Lys Gln Asn Pro Asn Val
145 150 155 160

Lys Met Gly Gly Arg Tyr Ala Pro Arg Asp Cys Val Ser Pro His Lys
165 170 175

Val Ala Ile Ile Ile Pro Phe Arg Asn Arg Gln Glu His Leu Lys Tyr
180 185 190

Trp Leu Tyr Tyr Leu His Pro Val Leu Gln Arg Gln Gln Leu Asp Tyr
195 200 205

Gly Ile Tyr Gly Ile Tyr Val Ile Asn Gln Ala Gly Asp Thr Ile Phe
210 215 220

Asn Arg Ala Lys Leu Leu Asn Val Gly Phe Gln Glu Ala Leu Lys Asp
225 230 235 240

Tyr Asp Tyr Thr Cys Phe Val Phe Ser Asp Val Asp Leu Ile Pro Met
245 250 255

Asn Asp His Asn Ala Tyr Arg Cys Phe Ser Gln Pro Arg His Ile Ser
260 265 270

Val Ala Met Asp Lys Phe Gly Phe Ser Leu Pro Tyr Val Gln Tyr Phe
275 280 285

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Gly Gly Val Ser Ala Leu Ser Lys Gln Gln Phe Leu Thr Ile Asn Gly
    290                 295                 300

Phe Pro Asn Asn Tyr Trp Gly Trp Gly Gly Glu Asp Asp Asp Ile Phe
305                 310                 315                 320

Asn Arg Leu Val Phe Arg Gly Met Ser Ile Ser Arg Pro Asn Ala Val
                325                 330                 335

Val Gly Arg Cys Arg Met Ile Arg His Ser Arg Asp Lys Lys Asn Glu
            340                 345                 350

Pro Asn Pro Gln Arg Phe Asp Arg Ile Ala His Thr Lys Glu Thr Met
        355                 360                 365

Leu Ser Asp Gly Leu Asn Ser Leu Thr Tyr Gln Val Leu Asp Val Gln
    370                 375                 380

Arg Tyr Pro Leu Tyr Thr Gln Ile Thr Val Asp Ile Gly Thr Pro Ser
385                 390                 395                 400
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